FILE COPY

UNITED STATES FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH
Office Of Therapeutics Research And Review
Division Of Clinical Trial Design And Analysis

Memo To: **The File, BLA # 97-0200**

Subject: **Medical Officer's Review**

Reviewer: Dina S. Stolman, M.D., Clinical Reviewer, General Medicine Branch

Through: Marc Walton, M.D., Ph.D., Branch Chief, General Medicine

Karen Weiss, M.D, Director, Division of Clinical Trial Design & Analysis

Date: October 15, 1997

Contents

This review document contains five individual Medical Officer reviews, as follows:

The table of contents appears on pages 1-3. Reviewer comments and conclusions for each review are included within the individual reviews.

I. OVERVIEW

A. Abciximab (ReoPro) is the Fab fragment of the chimeric monoclonal antibody c7E3. It binds with high affinity and specificity to the to the platelet glycoprotein (GpIIbIIIa) receptor of human platelets and inhibits platelet aggregation. In animal models of arterial injury, ≥ 80% blockade of platelet GP IIb/IIIa receptors prevented arterial thrombosis. Clinical studies have identified dose regimens that achieved and sustained 80% blockade and inhibited platelet aggregation.

B. Clinical Settings
Platelets are thought to play a significant role in the initiation of arterial thrombosis. Initial investigations began with the agent in the setting of percutaneous transluminal coronary angioplasty (PTCA). The use of PTCA is an effective means of enlarging the lumen of coronary vessels with atherosclerotic narrowing. There is, however, a risk of abrupt closure of the treated artery during or soon after the procedure in approximately 10 to 20 % of PTCA patients, which may result in ischemic cardiac complications, including acute myocardial infarction and death in some patients. Abciximab has been developed for use in patients undergoing PTCA as an adjunct to present therapy for prevention of these ischemic complications.

C. EPIC trial results
Results of the EPIC (Evaluation of c7E3 for the Prevention of Cardiac Ischemic Complications) trial, the pivotal phase III trial upon which approval of c7E3 was based, showed:

> (1) in 2,099 PTCA patients at high risk for abrupt closure of the treated coronary vessel, c7E3 reduced the rate of primary events (a composite of acute MI, recurrent ischemia requiring urgent intervention, or death) at 30 days from 12.8% to 8.3% compared to placebo control. There was not a demonstrable benefit on mortality alone (the number of deaths was small, 12 each in the placebo and the bolus + infusion arms. Patients with unstable angina and patients at risk for acute myocardial infarction seemed to benefit the most from the use of c7E3 during and after PTCA.
>
> (2) the frequency of major bleeding events was increased over placebo (10.6% vs 3.3%, respectively were the non-CABG major bleeding rates in the bolus and infusion and placebo arms, respectively). Bleeding was found to be inversely correlated with weight; that is, low-weight patients had higher rates of bleeding ($p<0.001$). All treatment groups received heparin in a standard, non-weight-adjusted regimen, suggesting weight-adjustment of the heparin dose might be an important variable. A single dose of c7E3, consisting of a weight-adjusted bolus and non-weight-adjusted infusion, was used in the trial.

Central issues in the discussions between the agency and the company during the licensing of c7E3 involved the examination of factors which might reduce bleeding while not compromising efficacy. The company undertook to evaluate the roles of heparin dosage, weight adjustment of the heparin and ReoPro doses, and features of arterial sheath management in development of bleeding complications. A pilot trial, the PROLOG trial was completed; the EPILOG trial was the pivotal trial which followed.

D. Current Indication and Labelling

Abciximab (ReoPro) was licensed in December 1994 by the FDA for the adjunctive treatment of patients undergoing percutaneous coronary angioplasty (PTCA) who were at high risk for the development of abrupt closure of the treated artery and the development of subsequent cardiac ischemic complications. The regimen approved was that used in the EPIC trial, a weight adjusted bolus dose of 0.25 ug/kg administered 10 to 60 minutes prior to the start of the PTCA, followed by a fixed dose constant infusion of 10 ug/min for 12 hours. Abciximab was intended for use with concomitant anticoagulation; the regimens recommended were those used in the EPIC trial: aspirin 325 mg po within 2 hours of the procedure and daily thereafter, and heparin 10,000 to 12,000 units IV bolus prior to and boluses of to 3,000 units during PTCA to a maximum of 20,000 units. Heparin was continued for 12 hours following the procedure to maintain an a PTT of 1.5 to 2.5 times normal.

E. Results Of PROLOG Trial

This Phase II randomized trial of 103 patients evaluated adjustments in heparin dose and early or late removal of the femoral arterial sheath along with c7E3, which was given in a weight-adjusted bolus and non-weight-adjusted infusion for 12 hours from the start of PTCA, as was done in the EPIC trial. All patients received c7E3 plus either the "standard-dose" or "low-dose" heparin (approx 30% less; target PTT lower). The heparin adjustments are identical to those in EPILOG. "Early" sheath removal refers to removal within 6 hours of the PTCA; "late" removal refers to removal 18 hours after.

Results showed a similar primary endpoint rate in the standard and low-dose heparin groups, of 7.7% and 7.8%, respectively, (at 7 days) comparable to that observed in the EPIC trial, 8.3% (at 30 days). Only 2 patients had major bleeding complications in the trial, but when a composite of major and minor bleeding, hematoma > 5 cm and transfusions was examined, late sheath removal and standard dose heparin were associated with more bleeding.

F. Phase 4 Commitments

Objectives of the EPILOG trial included the phase 4 commitment to improve the risk to benefit comparison of the use of c7E3, and reduction of bleeding complications. Although not a phase 4 commitment sought by the Agency, the sponsor also hoped to broaden the labeling for c7E3 to include patients other than those at high risk of acute ischemic complications. They were advised to ensure that sufficient high-risk and low-risk patients would be enrolled to provide meaningful results for each subgroup by monitoring enrollment in the study.

Centocor also agreed to evaluate the success of platelet transfusions for patients referred for CABG after c7E3 and to evaluate the incidence of intracranial hemorrhage and stroke in a larger population by optimizing reporting in EPILOG.

II. EPILOG PROTOCOL

PROTOCOL TITLE: "A Phase III (IV) Randomized, Double-Blind, Placebo-Controlled Trial Evaluating 30-day and 6-month Clinical Outcome following Percutaneous Coronary Intervention in Patients Treated with c7E3 Fab Bolus Plus 12-hour Infusion Given with Either Standard-Dose Weight-Adjusted or Low-Dose Weight-Adjusted Heparin"

A. Investigators/Trial Organization and Management

The study was sponsored by Centocor, Inc., and managed jointly by the Cleveland Clinic Foundation and Duke University Medical Center. Principal Investigators were Harlan Weisman, M.D., of Centocor, Robert Califf, M.D., and Eric Topol, M.D., Chairman of the Cleveland Clinic Cardiovascular Coordinating Center , who along with Robert McCloskey, Centocor VP of Research, formed the Executive Committee,which was responsible for appointing a Safety and Efficacy Monitoring Committee to review interim data, and a Clinical Endpoint Committee to confirm cardiac and safety endpoint events, and for the final decisions on modifying or terminating the trial, based on the SEMC recommendation.

An Operations Committee supervised the conduct of the trial, and included Kate Cabot, MD and Harlan Weisman, MD (Centocor), and Drs Topol, Califf, and A. Michael Lincoff (Cleveland Clinic). An investigator committee including principal investigators from all study sites, met with the Operations Committee and served to make recommendations to the Executive Committee on trial related issues and publications.

B. Objectives

To evaluate the efficacy and safety of the combination of c7E3 bolus and infusion with either a standard-dose or a low-dose weight-adjusted heparin regimen in a broad population of patients (not limited to high-risk patients) undergoing percutaneous coronary intervention. The low dose heparin arm was included to test whether efficacy with ReoPro could be obtained with a reduced risk of bleeding by lessening the degree of heparin anticoagulation.

C. Trial Design

A Phase IV double-blind, placebo-controlled, randomized, parallel design trial was planned with 3 treatment arms, involving approximately 4800 patients at 80 US and Canadian centers.

D. Drug Administration

Patients undergoing percutaneous coronary intervention with an FDA-approved device were allocated randomly to one of three groups:

a) c7E3 Fab bolus and infusion plus "standard-dose" heparin (100 U/kg bolus to max 10,000 units for patients ≥ 100 kg), then Q 30 minute boluses or 10 U/kg/hr infusion adjusted to maintain ACT > 300 sec)

b) c7E3 Fab bolus and infusion plus "low-dose" heparin (70 U/kg bolus to max 7,000 units for patients ≥ 100 kg), then Q 30 minute boluses or 7 U/kg/hr infusion adjusted to maintain ACT > 200 sec)

c) placebo bolus and infusion plus "standard-dose" heparin (as above)

The bolus and infusion of c7E3 were weight-adjusted (0.25 mg/kg followed by 0.125 ug/kg/min to max 10 ug/min for patients ≥ 80 kg) and was the same for both c7E3 treatment arms. *(Reviewer's Comment: The EPIC regimen used the same weight adjusted bolus but a fixed dose infusion of 10 ug/min).* The ReoPro infusion was continued for 12 hours; the heparin was to be discontinued immediately at the end of the index procedure, but was allowed to be continued (blinded) through the 12 hour period, and then longer (open-label) if the investigator felt it was indicated.

(Reviewer's Comment: Heparin was actually discontinued after the index procedure in only 1,458 patients (53 % of the 2,752 with interventions attempted). The others had heparin continued for varying lengths of time, 90% for less than a total of 24 hours. This was balanced across treatment arms).

The study blind was maintained through the use of a "heparin coordinator" at each study site who monitored the actual heparin dosing and ACT values. These were not known to the site investigators or individuals involved in patient care.

E. Concomitant Medications:

1. **Heparin** was recommended to be discontinued immediately upon completion of the index procedure but may have been continued longer at investigator discretion; open label heparin was allowed if indicated after the 12 hour infusion was complete, to maintain the aPTT at 60 to 85 seconds

2. **Aspirin:** 325 mg po within 2 hours prior to the procedure and daily thereafter

3. **Other cardiac medications:** as per usual practice (nitrates, beta blockers, ACE inhibitors, etc.)

4. **Arterial sheath removal and vascular access site care:** it was recommended that the arterial sheath be removed within 4-6 hours of discontinuation of heparin, and in all cases when the ACT was < 175 or PTT < 50; it could be left in place longer at investigator discretion

F. Patient Population

The trial was intended to enroll "all comers" with coronary artery stenoses ≥ 60 % who were thought to be candidates for a percutaneous coronary procedure, excluding patients with acute coronary syndromes; i.e. patients who fit the EPIC inclusion criteria with acute myocardial infarction or unstable angina. Patients with and without high-risk morphologic characteristics (as defined in the EPIC trial) were included.

Allowable procedures included balloon angioplasty, "bail-out" STENT placement (for failure of balloon procedure), and some types of atherectomy; most patients in the trial were treated with balloon angioplasty. Primary STENT placement was not initially included in the study; there was a STENT substudy added which randomized 123 patients to treatment with either primary STENT placement or PTCA, across the 3 treatment arms of the EPILOG study. (See Section VIII of this review; the substudy patients are included in the primary analyses of overall efficacy and safety for the EPILOG study.)

1. **Inclusion:** Patients > 18 years with a **target artery stenosis greater than or equal to 60 % by visual estimation** who are referred for elective or urgent PTCA with an FDA-approved device.

2. **Exclusion: Unstable angina or acute MI by EPIC criteria** in preceding 24 hours, Significant bleeding risks, uncontrolled hypertension, oral anticoagulants, > 50% stenosis LAD in absence of patent bypass graft, Rotational atherectomy, Planned Stent implantation (amended to include), PTCA in previous 3 months, allergic risk factors.

Reviewer's comment: EPIC included patients with acute unstable angina (n=826) and within 12 hours of onset of acute MI (n = 66) and high risk morphologic characteristics (n=1206). The benefit in prevention of cardiac ischemic complications was greatest in the patients with unstable angina and acute MI, who were at highest risk for the development of ischemic complications. EPILOG did not include either the patients with acute unstable angina or acute MI.

G. Efficacy Endpoints

1. Primary **There were two co-primary endpoints.**
   (a) **Death, MI or urgent intervention:**
   A composite of any **one** of the following within **30 days:**
   - all cause mortality,
   - acute MI or reinfarction,
   - severe ischemia leading to urgent repeat PTCA or CABG (urgent defined as within 24 hours of last episode of ischemia; severe ischemia defined as rest pain ≥ 5 min, or new ST-T wave changes, acute pulmonary edema or ventricular arrhythmias or hemodynamic instability presumed ischemic in origin)

   (b) **Death, MI or repeat revascularization:**
   A composite of any **one** of the following within **6 months:**
   - all cause mortality,
   - acute MI or reinfarction,
   - repeat revascularization (any PTCA or CABG)

An overall comparison of the 3 arms using a logrank test was performed at both the 30 day and the 6 month timepoints. If significant, this was followed by pairwise comparisons of each ReoPro arm to placebo. Success was required on **one** of these primary endpoints (either the 30 day or the 6 month) compared to the placebo arm to demonstrate the efficacy of the treatment.

Reviewer Comment: The logrank test, a time-to-event analysis, was prespecified by the sponsor for the primary endpoint comparisons.. In the CBER analyses, the Fisher exact test statistic has also been computed on both the 30 day and 6 month primary endpoints to compare the incidence of endpoint events among treatment arms.

2. Secondary
   (a) 6-month angiographic outcome (an angiographic substudy was to be done with 900 patients)
   (b) Death, MI, or target vessel revascularization within 6 months (any vessel treated initially)
   (c) Death, MI, or revascularization for clinically significant myocardial ischemia (unstable angina, recurrent stable angina or a positive functional test) within 6 months (includes urgent and repeat revascularizations for documented ischemia within 7 days of endpoint MI)
   (d) Health economic analysis of cost-effectiveness of rx

Reviewer Comment: Analysis of efficacy by risk subset was prespecified in the analytic plan but not the protocol.

H. Safety Endpoints

1. Primary
   (a) **Death and hemorrhagic stroke** incidence over the 6 month duration of the trial

   (b) **Major bleeding events not associated with CABG** during hospitalization or within 7 days, whichever is earlier (by TIMI study criteria).

2. Secondary
   (a) Nonhemorrhagic stroke,
   (b) Incidence of major bleeding in c7E3 vs. placebo arms,
   (c) Maximum decrease in Hemoglobin from baseline,
   (d) Minor bleeding event incidence by TIMI criteria,
   (e) Maximum Hemoglobin decline in patients having CABG during hospitalization,
   (f) Incidence of serious adverse events thought related to bleeding,
   (g) Incidence of bleeding requiring surgical intervention,
   (h) Incidence of major bleeding by age and gender,
   (i) Association of change in Hemoglobin with weight
   (j) Maximum change in platelet count,
   (k) Incidence of thrombocytopenia,
   (l) Incidence and type of transfusions,
   (m) Incidence of other adverse events.

I. Patient Enrollment

Patients were stratified for randomization by the presence or absence of high-risk clinical and morphological characteristics in the artery to be treated. Any one of the following combinations designated a patient's status as high risk:

- Female, age ≥ 65 years, and stenosis with at least 1 Type B characteristic (B1),
- Diabetes mellitus and stenosis with at least 1 Type B characteristic (B1)
- Stenosis with 2 or more Type B characteristics (B2),
- Stenosis with 1 or more Type C characteristics, (C) or
- Angioplasty of an infarct-related lesion within 7 days following acute MI (documented by CK-MB elevation).

Lesion classification is based on the ACC/AHA classification scheme. Type A, B and C characteristics are based on assessments by angiography of vessel tortuosity, accessibility of lesion, presence or absence of thrombus, calcification, and other criteria. (See Appendix 1)

The protocol specified the expected enrollment of 40% high risk patients and 60% lower risk patients by this scheme. At randomization, the lesion assessment was based on the clinical history and a general evaluation (see Appendix 2) of whether Type B or C characteristics were present upon review of the screening angiogram by the investigator (in some cases, only films from a referring cardiologist were reviewed).

After the index procedure was performed, and in some cases after the patient's hospital discharge,a detailed description of lesion morphology was completed on the case report form. On the CRF details were recorded as to the nature and extent of calcification, presence or absence of thrombus, the length and tortuosity of the vessel segment, and accessibility of the lesion. These details provided a more complete assessment of the anatomic features of the vessels that were treated.

Reviewer Comment: The CRF was to have been completed based on the pre-procedure assessment of the patient's clinical and lesion morphology characteristics. However, the CRF was completed at anytime up to 3 weeks after the procedure, with knowledge of the outcome of the procedure, and in some cases, knowledge of the patient's subsequent clinical course, and may have been influenced by these factors.

J. Randomization was performed at the Duke University Coordinating Center. A 24-hour telephone hotline was used. When a site called to randomize a patient, responses to questions on inclusion and exclusion criteria were entered into a computer system that identified kit numbers available at the site and the kit to be dispensed. Centocor and participating physicians did not have access to the code. All randomization was done centrally, with stratification by risk status, study site and whether or not a patient was participating in the STENT substudy. Certain sites also enrolled patients in the Angiographic Substudy; all patients at those sites were enrolled in the substudy. The randomization code was created by the Duke University Medical Center Department of Clinical Epidemiology and Biostatistics.

K. Blinding Study agent vials were labeled at Centocor, and shipped to Duke. The Duke University Core Pharmacy performed blinding, numbering and assembly of treatment kits, and assignment of kits to sites. Core Pharmacists had access only to data linking vials numbers to treatment assignment and vial numbers to study site, but did not have access to data linking vial numbers to patients. Unblinding could only be initiated by an investigator, in case of an emergency, for an individual patient, by cutting the label on the vial. The label was then placed in the patient's CRF, and the page forwarded to the data monitoring group to be kept in a locked cabinet until trial completion.

Heparin coordinators were assigned at each study site to maintain the blind to treatment arm assignment for members of the investigational team. Only the heparin coordinator at the study site knew the ACT and PTT values, and directed the changes in heparin dosage/ administration throughout the time of study agent administration. The heparin coordinator was not allowed to make study related observations other than recording the ACT measurements or heparin dosage adjustments. The CRF pages (15 and 16) with the heparin and ACT data were sequestered until trial completion. If blinded heparin was continued after the index intervention, the heparin coordinator was responsible for starting the infusion in the cath lab; later adjustments to the infusion rate were made on a volumetric basis by other individuals based on PTT only without knowledge of the actual dose being administered, as only the heparin coordinator knew the concentration.

HACA data was analyzed at Centocor. A separate recording and tracking system was used for these data to maintain the blind. All samples, through 6 months were to be shipped and run at the same time.

In some cases, open label use of commercial ReoPro was allowed at investigator discretion. In such cases, if prior to completion of study agent infusion, the investigator was to unblind the study agent to determine if a ReoPro bolus was needed, and note the date and time of discontinuation of study agent. These data were recorded on a separate CRF page and sequestered until trial completion.

L. Calendar of Assessments

The screening history and labs, including CBC, platelet count, PT, PTT, BUN, and creatinine were to be done within 7 days prior to randomization. Within 2 hours prior to randomization, another vital signs reading was taken, and CPK, CPK-MB, EKG, Hemoglobin, Hematocrit, BUN and creatinine.

Study drug was to be administered within 10 to 60 minutes prior to the start of the index procedure. Heparin and aspirin were initiated and continued per protocol. For patients who were pretreated with heparin prior to the start of study agent, this non-study heparin was to have been discontinued at least 5 minutes prior to the baseline ACT. Prior to each angiogram, the patient received 100 to 300 ucg of intracoronary nitroglycerine as a vasodilator.

A scout angiogram was typically performed prior to the procedure, and followed by the procedure itself, which took from twenty to sixty minutes (a smaller number of more technically difficult procedures were prolonged to up to ninety minutes).

Assessments after the procedure included vital signs q one hour x4, then q 6 hours x 4, timed from the bolus of study agent, EKGs on arrival to the ward and daily thereafter while hospitalized, at 30 days and at 6 months, platelet counts at 30 minutes, and at 2, 12, and 24 hours after the bolus, then daily until day 3. Platelet counts were obtained for any at discharge values < 150, 000, at 30 days and 6 months. Any platelet counts of < 100,000 were repeated and verified in a citrated tube, and counts redetermined at 2 and 4 hours. Verified thrombocytopenia was followed with daily platelet counts until platelets returned to > 100,000 and within 25 % of the baseline value. For platelet counts below 60,000, heparin, aspirin, and study agent were to be discontinued. Transfusion of platelets was recommended if the platelet count dropped below 50,000.

Hemoglobin and hematocrit were done at 12 hours after the study agent bolus. Other laboratory assessments at 36 hours after bolus or prior to discharge included CBC, platelets, PTT, BUN and creatinine. For patients discharged more than 60 hours after the bolus, the same labs were to be repeated at 60 hours.

During the procedure, ACT was monitored as described elsewhere. The ACT or aPTT was to be obtained immediately prior to sheath removal, and the sheath was only to be removed when the ACT was < 175 or the PTT < 50. Patients who were to have study heparin continued after the procedure were to have a PTT at 6 hours after completion of the procedure for adjustment of the heparin infusion. Cardiac enzymes were obtained at 2 hours, then q 6 hours from study agent bolus through 24 hours, then q 8 hours for 48 hours or until discharge.

Post procedure angiograms were performed at the conclusion of the index procedure on all patients. The patients entered in the Angiographic Substudy were to undergo repeat coronary angiography at 6 months (184 to 275 days post randomization). The angiography was encouraged to be performed at the same institution, and catheter size and procedures specified.

Human anti-chimeric antibody (HACA) responses were evaluated at 7 days or discharge, 30 days, and 6 months following treatment for all patients in the angiographic substudy.

M. CRF and Field Monitoring

(1) the Medical Monitor Reviewer was [redacted] an attending cardiologist at [redacted] his duties included review of 30 day CRFs to identify possible adverse or endpoint events and clinical abnormalities or inconsistencies on the CRFs needing clarification.

(2) Field monitoring of CRFs and monitoring of sequestered heparin dosing and ACT data were performed by a CRO, the [redacted] An independent data management group, [redacted] was responsible for entry and query of the sequestered CRF data.

N. Interim Safety and Efficacy Monitoring

Interim data review was performed by an external Safety and Efficacy Monitoring Committee, which was independent of the sponsor. Members included cardiologists :

The Committee was to perform Interim Analyses after 1500 and 2500 patients had been enrolled. The primary endpoint was death or MI within 30 days, to ensure that the efficacy of the treatment was not reduced in the low dose heparin arm, resulting in higher numbers of cardiac events in those patients. Efficacy data were only available to the committee at the Interim Analysis, and not for continuous efficacy monitoring. Serious adverse events thought reasonably related to study agent were also monitored by the SEMC on an on-going basis.

SEMC recommendations to stop the trial were transmitted initially to Dr. McCloskey and Dr. Califf. Dr. McCloskey was to notify the FDA and then inform the full Executive Committee, which was responsible for determining whether to accept the recommendations. Written records of all communications were to be kept and held in escrow until the end of the trial.

The Biostatistics Department at the Cleveland Clinic had primary responsibility for interim data analyses and presentation to the SEMC. The Statistician was a non-voting member of the SEMC. Centocor was responsible for final data analyses after completion of the study.

O. Endpoint Assessment

1. A **central Clinical Endpoint Committee** reviewed CRFs, EKGs and other supporting data or clinical tests results (e.g. CT scan, CK values, Hb, Hct, discharge summaries and operative notes) on all patients suspected of having all primary and some secondary 30 day and 6 month cardiac endpoint events, deaths, all strokes and major and minor bleeding events. Patients were flagged for CEC review with possible endpoint or bleeding events using computer screens. The CEC coordinator or one of 5 co-coordinators reviewed all cases that were not flagged for CEC review to determine if an endpoint may have occurred; any of concern were then forwarded to the CEC.

The role of the CEC was to confirm the occurrence of these events. CEC review was blinded to treatment group. Agreement of a minimum of 2 CEC reviewers was required to rule in an endpoint or event.The CEC at the Cleveland Clinic was composed of 23 cardiologists, 17 noninterventional cardiology fellows, and 6 noninterventional cardiology staff members. The CEC at Cleveland Clinic reviewed data on all patients from all other enrolling sites. A supplementary CEC was set up at Duke University Medical Center to review patients enrolled at the Cleveland Clinic. None of the CEC members were investigators in the trial.

A Cleveland Clinic neurologist, Cathy Sila, M.D., reviewed and adjudicated all cases of suspected stroke. Dr. Sila was provided with CRF data and copies of contrast CT or MRI scans.

2. A **central EKG Core laboratory** reviewed all EKGs for the presence of Q waves. This blinded review identified patients with possible Q wave MI that may have been missed by other screening procedures. The CEC was informed of the EKG Core Lab's readings on cases it reviewed. EKG's at all timepoints were reviewed: baseline, 7 days or hospital discharge, 30 days, and 6 months.

3. The Angiographic Core Lab at the Cleveland Clinic Cardiovascular Coordinating Center reviewed all coronary angiograms for patients enrolled in the Angiographic Substudy. All patients at certain sites were enrolled in this substudy; these patients underwent repeat coronary angiograms at 6 months post randomization. The core lab independently assessed the extent of coronary disease, target vessel and lesion morphology, quantitative luminal dimensions, and results of the index procedure at the 6 month timepoint. The objective was to assess the effects of Abciximab on restenosis.

Assessment was blinded to treatment group. Two reviewers were to assess each case, and disagreements were to be resolved by the laboratory Medical Director. Some of the members were investigators, but they were not allowed to review data on their own patients. A total of 286 patients was enrolled in this substudy; it was planned for

P. Planned Statistical Analyses

1. **Interim Analysis** A planned Interim Analysis was performed at 1500 patients. The primary endpoint for the Interim Analysis was death and MI at 30 days; the primary reason for this interim was to be sure that the low dose heparin arm did not result in a higher rate of cardiac events (reduced efficacy).

Pairwise comparisons were made between each of the Abciximab arms and the placebo arm. Unequal stopping rules were invoked for the interim analysis; a stricter criterion was required to halt the trial for efficacy than for safety reasons. The trial was to be stopped for a p=.025, one-sided if an experimental arm had a higher rate of death or MI than placebo, and for a p=.0005 if an experimental arm appeared better than placebo. Descriptive statistics were to be used to analyze bleeding complications.

The protocol called for a second interim analysis at patients at the discretion of the SEMC, however the trial was halted after the analysis on the 1500 patients. The analytic plan called for the interim analysis primary endpoint of death and MI at 30 days to become the primary endpoint for the determination of efficacy at the final analysis, if the study was halted for efficacy at the interim analysis. In this event, the 3 part composites specified at 30 days and at 6 months would become secondary endpoints.

2. **Final Analysis**

An overall test for any significant difference among treatment arms was performed first at the final analysis. This was a generalized logrank test , time from randomization to event recorded; patients censored who do not reach endpoints in observation period) and significance was required at a one-sided p value of .0287 for any difference among treatment arms.

If the screening test was significant, then pairwise comparisons were performed of each of the ReoPro arms to the placebo arm, also using a logrank test. Significance was required at a $p < .05$ (one-sided) on one of the primary efficacy endpoints. Both the 30 day and 6 month primary endpoints were analyzed in this way.

Q. Amendments to Protocol and Analytic Plan

An amendment specifying the planned proportion of high and low risk patients to be enrolled was put in place before the trial commenced in February 1995. Minor protocol changes (laboratory monitoring) were made once the trial was underway. A protocol for the Angiographic Substudy was submitted prior to the enrollment of patients at those sites, shortly after the trial began. The protocol for the STENT substudy was put in place in June, 1995, and the substudy, at 17 sites, began enrolling patients for primary STENT placement in August 1995.

R. Definitions

The following definitions were used in the trial, and are provided here to aid the reader in understanding the terminology used:

1. *Baseline disease*--clinical diagnosis of unstable angina not fulfilling EPIC criteria includes:
   1) angina at rest within the previous month or
   2) new onset exertional angina of less than two months duration or
   3) severe or frequent (≥ 3 times/day) exertional angina or
   4) accelerated angina (exertional angina that is more frequent or precipitated by less exertion).

2. *Target vessel* is any vessel to be treated during the index procedure.

3. *Severe myocardial ischemia requiring urgent repeat intervention* (the 30-day primary endpoint): One or more episodes of rest pain, presumed ischemic in origin and lasting at least 5 minutes, which result in either urgent repeat PTCA or CABG surgery.
   a) To be considered urgent the repeat procedure must be initiated within 24 hours of the last episode of ischemia.
   b) In the absence of pain, the following were sufficient evidence of ischemia: new ST or T wave changes, acute pulmonary edema, or ventricular arrhythmias presumed ischemic in origin.

4. *Repeat revascularization for clinically significant recurrent myocardial ischemia* (the 6 month primary endpoint) :

Includes 1) Any repeat revascularization procedure (PTCA or CABG) performed for any of the following reasons:
   a) Unstable angina, defined as in 1. Above,
   b) Recurrent stable angina,
   c) Positive functional test (ETT showing ≥ 1 mm horizontal or downsloping ST depression at 80 msec after the J point, or Perfusion or metabolic scintigraphy showing reversible defect on exercise or pharmacologic stress testing, or ECHO or MUGA showing reversible wall motion abnormalities during stress testing)
   2) Repeat revascularization within 7 days of endpoint MI
   3) Urgent revascularization for severe myocardial ischemia.

III. STUDY POPULATION

A. Study Dates and Enrollment

Enrollment ran from February 29, 1995 through December 14, 1995, when the trial was terminated for efficacy at the recommendation of the SEMC.
The trial was discontinued after the 1500 patient interim analysis as the efficacy parameter exceeded the prespecified threshold for the ReoPro treated arms; there was evidence of both reduced bleeding and of improved efficacy in the ReoPro arm with low dose heparin. At that point the enrollment was 2792 and the final analysis was performed. The sponsor notes that the Interim Analysis serves as their primary analysis of efficacy and safety, however.

(Reviewer's Note: SEMC records have been reviewed; it appears appropriate procedure was followed.)

B. Baseline Characteristics

1. Demographics

The study arms were well balanced with respect to age, gender, height and weight and race. Approximately 70% of patients in the study were male, with a median age of 60 years. Ninety percent were Caucasian, 6% Black, 2% Hispanic and less than 1% each of other races. (see Table 1 on next page for a listing of baseline patient characteristics in all treatment arms.)

2. Cardiac History

More than half of the patients enrolled had a history of unstable angina, and 50% had a history of MI, 18% had an acute MI within 7 days. Patients with acute coronary syndromes (acute MI within 24 hours or active unstable angina at presentation) were excluded, however. (see Table 1). Only 1.6 % of patients had a history of congestive heart failure, and 2 % had a history of any type of previous cerebrovascular accident (only 3 patients had a prior hemorrhagic stroke). All these were well balanced among treatment groups.

3. Indication for the Index Procedure

Nearly half the patients enrolled were referred for the index procedure because of unstable angina; 20% for recent MI *(reviewer's note: MI may have been within 7 days but not 24 hours; acute unstable angina was also excluded)*. (See Table 1). A positive functional test was the primary indication in one quarter of patients. These percentages were similar across treatment arms.

4. Type of Intervention

Most patients enrolled (76.4 %) underwent balloon angioplasty only; 20 % of patients underwent other percutaneous procedures, including directional atherectomy (144), rotational atherectomy (15), Laser (14), TEC atherectomy (8), and 56 were randomized to coronary STENT placement. Another 326 patients underwent bail-out STENT placement (124, 81 and 121--least in the ReoPro Low Dose Heparin arm). STENT results are presented separately elsewhere in this report. Three percent of the index interventions were urgent procedures. Among other interventions, thrombolytics were used in only 9 patients in the trial. (See table 1 on next page.)

Table 1 Selected Baseline Characteristics[1]

Characteristic	Placebo n= 935	Reo + Lo Hep n= 939	Reo + Std Hep n = 918
Demographics			
Male (%)	674 (71.8)	668 (71.4)	670 (73.0)
Median Age, yrs (range)	60 (29, 80)	60 (31, 87)	60 (31, 85)
Median Weight, kg (range)	83.6 (46, 156)	84 (45, 163)	84 (44, 164)
History			
MI within 7 days (%)	170 (18.1)	170 (18.2)	156 (17.0)
Diabetes (%)	224 (23.9)	212 (22.7)	202 (22.0)
Prior CABG or PTCA	362 (38.6)	339 (36.2)	342 (37.3)
Indication for Procedure			
Unstable Angina (%)	474 (50.5)	434 (46.4)	420 (45.8)
Recent MI (%)	189 (20.1)	200 (21.4)	190 (20.7)
Chronic Stable Angina	56 (6.0)	61 (6.5)	53 (5.8)
Positive Functional Test	193 (20.6)	212 (22.7)	218 (23.7)
Intervention Type			
Balloon Angioplasty	889 (96.3)	886 (96.0)	873 (96.4)
Balloon only	705 (76.4)	751 (81.4)	702 (77.5)
Atherectomy	57 (6.1)	55 (6.3)	55 (6.1)
Urgent	33 (3.6)	24 (3.6)	34 2.8)

1 Only selected categories are included in this table

5. Risk Classification

Patients were stratified at randomization by the presence or absence of high-risk clinical and morphological characteristics in the artery to be treated. The protocol specified a projected enrollment of 40% high risk patients and 60% lower risk patients by this scheme. At the time of randomization, 64.4% of patients were thought to have high risk characteristics (balanced across arms), and only 35.6 % of patients were thought to be lower risk.

When risk status was assessed using the completed CRFs, over half of the patients determined to be lower risk at randomization were shifted to the higher risk category. This shift was balanced across treatment groups, and in fact, some patients shifted from higher to the lower risk category, but far fewer. By the CRF data, then, only 19 % of the patients in the trial were in the lower risk category. (See Tables 2a and 2b).

Table 2a Patients By Risk Classification At Time Of Randomization And By Risk Re-Classification Based On CRF Data

	Placebo + Std Hep n=939	ReoPro + Lo Hep n=935	ReoPro + Std Hep n=918
As Randomized			
High Risk Patients			
n	602	602	590
%	64.1 %	64.4 %	64.3 %
Low Risk Patients			
n	337	333	328
%	35.9 %	35.6 %	35.7
Based on CRF			
High Risk Patients			7
n	748	738	32
%	79.6 %	79.0 %	79.8 %
Low Risk Patients			
n	176	186	175
%	18.8 %	19.9 %	19.0 %
Unable to Classify			
n	2	5	2
%	0.2 %	0.5 %	0.2 %

Table 2b shows the total numbers of patients in the trial by risk status assessment at randomization and at CRF classification.

Table 2b High and Low Risk Patients At Randomization and By CRF

	Low Risk at Randomization n = 998	High Risk at Randomization n = 1794
Low Risk by CRF n = 537	391 39 %	146 8 %
High Risk by CRF n = 2218	598 60 %	1620 90 %
Unknown by CRF n = 37	9 0.9 %	28 1.6 %

The largest change occurred in the group categorized as low risk at randomization, shifting to high risk by the CRF. The majority of the changes were due to morphologic characteristics of the lesion which were categorized differently by the investigator at the time of CRF completion (see table 3a). There were 23 of these patients who changed due to clinical history only (diabetes or previous MI not recognized at the time of randomization).

Of those whose status changed due to lesion morphology reclassification, most were changed from B1 to B2; these patients were found to have an additional B characteristic in the treated lesion at the time of CRF completion (see table 3b). Changes occurred in all categories, however.

Table 3a Number of Patients Whose Risk Status Changed from Randomization to CRF Completion by Reason for Change in Risk Classification

Reason for Change	Low to High Risk (n = 598)	High to Low Risk (n = 146)
History of MI	14 (2.3 %)	6 (4.1 %)
History of Diabetes	9 (1.5 %)	1 (0.7 %)
Diabetes and Lesion Morphology	2 (0.3 %)	0
Lesion Morphology Only	573 (95.8 %)	139 (95.2 %)

Table 3b Number of patients by lesion morphologic change

Low to High Risk Morphologic change	Number of patients (%) n = 575	High to Low Risk Morphologic change	Number of patients (%) n = 139
B1 to B2	356 (61.9 %)	B1 to A	30 (20.5 %)
B1 to C	67 (11.7 %)	B2 to B1	63 (43.2 %)
A to B1	29 (5.0 %)	B2 to A	28 (19.2 %)
A to B2	81 (14.1 %)	C to B1	13 (8.9 %)
A to C	42 (7.3 %)	C to A	5 (3.4 %)

The most common lesion characteristics causing a change in status appear to have been length, eccentricity, accessibility, angulation, and contour (these were also the most common of the 11 criteria that were rated as B2 or C for all patients). The investigators were to have evaluated the screening angiograms by these same criteria at the time of randomization as at the time of CRF completion, but the individual characteristics were not required to be listed at the time of randomization. Only an overall assessment of the risk status based on lesion morphology and clinical factors(A, B1 or B2, or C) was made at randomization. The CRFs were usually completed after the procedure had been completed, or in some cases, after hospital discharge, up to 3 weeks after the procedure.

Reviewer Comment: The recording of lesion characteristics on the CRF was to have been performed based on the pre-procedural assessment. The hindsight of the procedural outcome (or subsequent clinical events) may have permitted a more complete assessment of the specific lesion characteristics, or in fact, a more biased assessment toward higher risk classification. See Appendix 2 and 3, for copies of the randomization profile and the CRF page on which this information was recorded.

Reviewer's Note: The possibility that bias may have entered into the assessment of risk status at the time of randomization has been considered as well. The sponsor has stated that only one letter was sent to the investigators encouraging the enrollment of low risk patients. That was after the interim analysis, and after most of the patients in the study had already been enrolled. The sponsor also stated that the percentages of low and high risk patients enrolled did not differ before and after the letter was sent. Copies of correspondence and investigator meeting agendas have confirmed all of these statements to be true.

B. Patient Disposition

1. Protocol Violations

A total of 48 patients (1.7 %) did not meet inclusion criteria. The proportion was similar across all 3 treatment groups (15 in the placebo arm, 17 in the Abciximab Low Dose Heparin arm, and 17 in the Abciximab-Standard Dose Heparin arm). All patients were included in the primary and secondary analyses of results. Most common reasons for violations included a PTCA within the previous 3 months (10) and Prothrombin Time greater than 1.2 x control (17). Others included hypertension (6), planned STENT (4), occlusion < 60 % (3), and a scattering of other reasons.

2. Treatment Received vs Randomized

The primary statistical analyses were all Intent-to Treat, and included all patients randomized. Of the total 2792 patients, 97.6% were actually treated with the study agent as randomized. A total of 67 patients, (2.4 % overall, balanced among arms) did not receive study agent at all. Table 4 presents the reasons patients were not treated. Administrative reasons (did not meet enrollment criteria, etc.) and the anticipated risk of bleeding were most frequent, followed by patients who did not have a target lesion with ≥ 60 % stenosis and patients who received alternate medical therapy. Four placebo patients and 1 ReoPro Low Dose Heparin patient underwent CABG following randomization and were not treated.

Table 4 Reasons Patients Were Not Treated (some patients had more than 1 reason given)

	Total n=74	Placebo n=32	ReoPro Std Dose n=20	ReoPro Lo Dose n=22
Risk of Bleeding	12	3	4	5
Occurrence of Bleeding	6	1	4	1
Other AE or Abnormal Lab	1	0	1	0
No target lesion ≥ 60%	7	4	1	2
Alternate medical rx	7	3	2	2
Rotational Atherectomy	4	1	1	2
Planned STENT	5	2	0	3
CABG	5	4	0	1
Consent Withdrawn	6	3	1	2
Administrative	18	8	6	4

Of the patients receiving study agent, 10.3 % did not receive the full dose (balanced among arms) and some of those patients, (a total of 4.6 % in the study) received neither the full dose nor the protocol specified rate of administration due to nursing error or miscalculation. The largest number of patients are shown in the "Administrative" category in all three treatment arms. Deviations from the total dose and from the protocol-specified rate were minor and resulted in only minor deviations from the protocol specified time of 12 hours of administration of the infusion. (See Table 5).

Reviewer's Note: The sponsor was asked for information on the amount of deviation from the planned dose in the cases attributed as "administrative" by treatment arm. Details were provided on the 32 patients in the Abciximab Standard Dose arm and on the 27 patients in the Abciximab Low Dose Heparin arm. Nearly all of the deviations of rate of administration were minor (1-2 cc/hr, resulting in administration times a bit shorter or longer than the protocol-specified 12 hours). Ninety percent of these patients received > 90 % of the planned dose. The remaining patients all received > 73 % of the planned dose. These data appear to have had no significant impact on the study results.

Table 5 Reasons Patients Did Not Receive Full Dose (treated patients; some had more than 1 reason)

	Total n=2725	Placebo n=913	ReoPro Lo Dose n=915	ReoPro Std Dose n=897
Patients not receiving full dose[1]	280 10.3 %	100 11.0 %	82 9.0 %	98 10.9 %
Patients not receiving infusion at a constant rate[2]	125 4.6 %	51 5.6 %	31 3.4 %	43 3.8 %
Risk of Bleeding	8	2	4	2
Occurrence of Bleeding	52	10	16	26
Thrombocytopenia	5	0	1	4
Other AE or Abnormal Lab	28	8	8	12
No target lesion ≥ 60%	8	3	3	2
Alternate medical rx	13	8	2	3
Rotational Atherectomy	4	2	1	1
Planned STENT	29	16	4	9
Failed PTCA	62	21	22	19
CABG	28	12	4	12
Death	1	0	0	1
Administrative	96	37	27	32

1 Study agent was discontinued after treatment was begun
2 A subset of the total; the actual rate of study agent administration varied from the protocol specified rate.

3. Completeness of Follow Up

The 30 day endpoint assessment required ≥ 27 days followup. A total of 84 patients (3 %) in the trial had incomplete follow up at the time of the 30 day database lock and had not experienced an endpoint event. These were evenly distributed across treatment arms. (see Table 6).

Most cases of missing 30-day data (64 of the 84) were due to early follow-up visits. Over half of these patients (45) had at least 20 days followup. The reasons for the early followup visits are unknown, as they were not recorded on the CRFs. Seventeen (17) patients of the remaining 20 were subsequently located by the time of the 6 month database lock, so that all but 3 patients had complete 30 day followup at that time.

All patients with early 30 day visits had complete 6 month followup. There were only 3 patients who were lost to followup prior to 30 days who were also missing at 6 months. There were 12 patients (0.4 %) who did not have complete 6 month follow up (defined as followup < 165 days and no event prior to last followup).

Table 6 Patients With Incomplete Follow-Up[1]

	Placebo n = 939 n (%)	Reo + Lo Hep n = 935 n (%)	Reo + Std Hep n = 918 n (%)
< 27 days	30 (3.2)	30 (3.2)	24 (2.6)
< 165 days	3 (0.3)	3 (0.3)	6 (0.7)

1 at the time of the database locks at 30 days and 6 months

(Reviewer's Note: In response to an information request, the sponsor submitted a reanalysis of the 30 day primary endpoint results using the 6 month database (including the 17 patients not included in the 30 day database). The missing data do not have significant impact on the results.)

4. Heparin Administration and ACT Values

The protocol specified adjustment of the heparin infusion to maintain an ACT during the procedure of greater than 200 seconds, and of greater than 300 seconds in the standard dose heparin and the placebo arms. There was a difference of 46 seconds on median ACT values between the placebo and the Abciximab-low dose heparin arms, and a difference of 78 seconds between the Abciximab-low dose heparin and the Abciximab-standard dose heparin arms; the protocol appears to have been followed with regard to heparin dosing. The ACT values were a little higher in the Abciximab-standard dose heparin patients than in the placebo arm, which used heparin in the standard doses alone. In Table 7, "pre-device" refers to after the bolus and infusion of study drug and just prior to use of the balloon or other device during the procedure.

Table 7 ACT Values During Index Procedure

Patients With Intervention Attempted	Placebo n = 923	Reo + Lo Hep n = 923	Reo + Std Hep n = 906
ACT pre-device (sec)	329 (311, 358)*	283 (246, 324)*	361 (326, 402)*
Max during procedure (sec)	340 (320, 378)*	299 (263, 345)*	375 (343, 425)*

* Median, Interquartile range

The maximum ACT shows a similar difference, as well, in the median values and in the interquartile range, indicating that there were many in the ReoPro Standard Dose Heparin arm who had maximum ACTs above 400. All ACT values for the ReoPro low Dose Heparin arm were most often below 300 seconds, as the protocol had specified.

Reviewer Comment: The ACT values in the Abciximab-standard dose heparin arm were consistently a bit higher than those in the placebo-standard dose heparin arm, suggesting the higher ACT was more easily achieved in the presence of Abciximab.

5. Study Treatment Unblinding

Unblinding occurred in 167 patients total in the trial (6 %); a bit more often in the placebo arm than in either ReoPro arm. Most of these involved unblinding of ACT values only.

Table 8 Unblinding Of Treatment

	Placebo n = 939	Reo + Lo Hep n = 935	Reo + Std Hep n = 918
Any Unblinding	75	40	52
Heparin Unblinding	9	6	10
Study Agent Unblinding	15	3	13
ACT Unblinding	69	36	45

Note: some patients may be listed more than once

Unblinding of study agent occurred in a total of 31 patients (1.1 %) in the trial, fewer in the ReoPro Lo Dose arm, but all numbers are small. Heparin was unblinded in 25 patients total. ACT was unblinded in 150 patients. Of the 150 patients who had ACT unblinded, only 28 also had study agent or study heparin unblinded. The most common reason for unblinding was the necessity for understanding the coagulation status of a patient to undergo CABG; followed by STENT placement, particularly in the Placebo and Reo Std Dose arms (there were more patients going to CABG and receiving STENTS in these arms). There were 2 patients unblinded because of hemorrhagic stroke (one in each of the ReoPro arms) and 1 pericardial tamponade (in the Reo Std Dose arm).

6. Patients Who Did Not Have Index Intervention

A small number of patients enrolled did not have the index intervention performed (see Table 9) Lack of a significant lesion with > 60% stenosis was the most common reason, followed by CABG or alternate medical therapy and administrative reasons. One patient in each of the ReoPro arms did not have the procedure because of bleeding.

Table 9 Patients Who Did Not Have Index Intervention (not a complete list)

	Placebo	Reo + Lo Hep	Reo + Std Hep
Patients not having intervention	16	12	12
No Significant Lesion	7	4	4
CABG or Other Medical Therapy	7	3	4
Bleeding	0	1	1
Other	2	4	4

7. Sites

Of — sites planned, 69 sites actually enrolled patients. There were 58 US sites, accounting for 2,681 patients, and 11 Canadian sites, accounting for the remaining 111 patients. A total of 18 sites enrolled more than 50 patients; of these, only one enrolled more than 200 (201); 5 sites enrolled between 123 and 176 patients, 12 sites enrolled 50-100 patients and 27 sites enrolled between 20 and 50 patients. The remaining 22 sites each enrolled between 1 and 18 patients. There were 29 academic sites enrolling a total of 814 patients and 39 non-academic sites enrolling 1,977 patients.

IV. EFFICACY RESULTS – PRESPECIFIED ANALYSES

A. Primary Endpoints

(Reviewer's note: primary prespecified analyses only included the overall composite rates; rates by component are also presented here for continuity)

1. 30-Day Primary Endpoint composite and by component

The 30 day primary endpoint was a composite of all cause mortality, myocardial infarction (MI), and urgent repeat revascularizations for severe myocardial ischemia occurring during the 30 days post randomization. The overall test for any significant difference among the three treatment arms had a p value of < .0001. Pairwise comparisons showed a significant treatment effect in both the ReoPro arms on the composite primary endpoint compared to placebo; the composite endpoint occurred in 11.7 % of placebo patients and in 5.2 and 5.4 % of ReoPro treated patients, in the Low Dose and Standard Dose Heparin arms, respectively. The largest effects of ReoPro over placebo were seen in the occurrence of MI's and of urgent revascularizations. There was no significant difference in mortality between the arms, although there were a lower total number of deaths in the ReoPro treated patients.

Table 10 (see next page) presents the number and percentage of primary endpoint events by treatment arm for the composite and by component.

Figure 1 (see following page) presents the Kaplan Meier curves for the time to event data on the primary composite endpoint.

Table 10 All Randomized Patients 30 Day Primary Endpoint[1]

		Placebo n=939	ReoPro + Lo Hep n=935	ReoPro + Std Hep n=918
Death, MI, or Urgent Revascularization	n % 95 % CI p value[2] p value[4]	109 11.6 % (9.56 - 13.66)	48 5.1 % (3.72 - 6.55) < .0001 < .0001	49 5.3 % (3.88 - 6.79) < .0001 < .0001
Death	n % 95 %CI[3] p value[2] p value[4]	7 0.8 % (0.20 - 1.30)	3 0.3 % (-0.04 - 0.68) .1 .3	4 0.4 % (0.01 - 0.86) .2 .5
MI	n % 95 % CI[3] p value[2] p value[4]	81 8.7 % (6.83 - 10.42)	34 3.7 % (2.44 - 4.84) < .001 < .0001	35 3.8 % (2.57 - 5.05) < .001 < .0001
Urgent Revascularization	n % 95 % CI[3] p value2 p value[4]	48 5.2 % (3.70 - 6.52)	15 1.6 % (0.80 - 2.41) < .001 < .0001	21 2.3 % (1.32 - 3.25) < .001 = .0013

1 For the log rank test on the composite, patients were counted only once by most severe component For the analysis by component, patients may have been counted more than once. All events were counted; patients who had more than one event are listed once for each event.

2 1 sided p values calculated for time-to-event analysis using Logrank test, sig < .05, comparison to placebo

3 95 % CI as per CBER Biostatistics review

4 2 sided p value calculated using Fisher's exact test, per CBER Biostatistics review

Figure 1 Kaplan-Meier Curve For 30 Day Time To Event Data

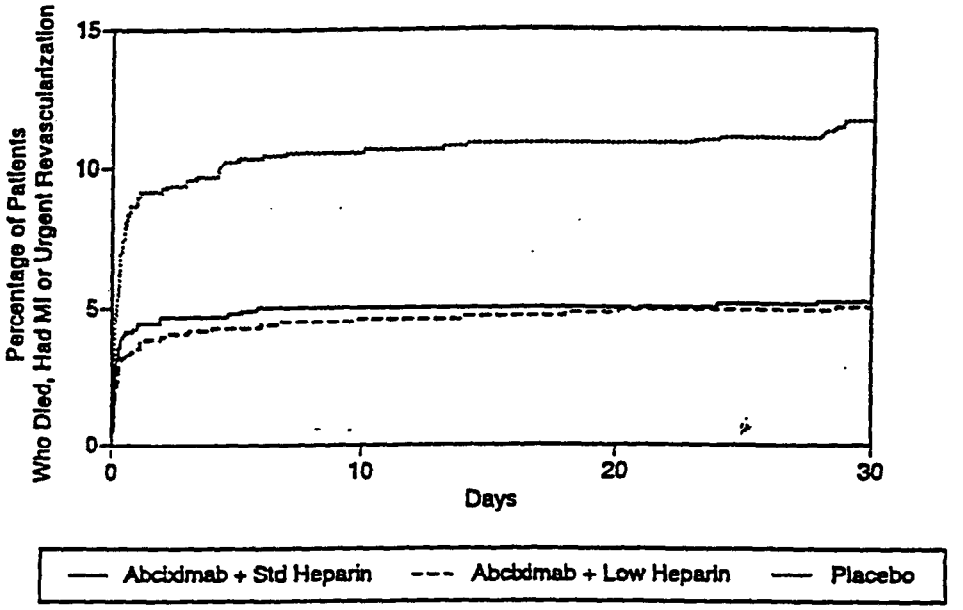

Figure 3 Kaplan-Meier Event Rates for Death, MI or Urgent Revascularization Through 30 Days in Randomized Patients (individual abciximab treatment groups are shown).

2. 6 Month Primary Endpoint composite and by component

The p value for the overall comparison is .015; it was required to be < .0287. Pairwise comparisons were then performed on each Abciximab treatment arm compared to placebo. A small advantage was seen for the ReoPro treated patients. The difference on this composite endpoint is statistically significant by the sponsor's analysis, but is less so than that seen on the 30 day primary endpoint. When the Fisher exact test is used, there is no statistical significance seen between the ReoPro arms and the placebo arm on this endpoint. (See table 11).

MI at 6 months is significantly reduced in the ReoPro arms, by both logrank and Fishers methods. and there is a trend to reduced deaths though the numbers are small and it does not reach statistical significance.

There was no significant difference in all repeat revascularization procedures among treatment arms at the 6 month endpoint. Rates for all revascularization catch up in the ReoPro arms to placebo rates by 6 months. This was due largely to similar rates for revascularization procedures that were not urgent among the treatment arms. There was still a trend toward improved rates of urgent revascularizations (see Table 28 in Section VB of this review).

Table 11 6 Month Primary Endpoint Composite and by component [1]

Patients		Placebo n=939	ReoPro + Lo Hep n=935	ReoPro + Std Hep n=918
Death, MI, or Repeat Revascularization	n % 95 % CI [2] p value [3] P value [4]	241 25.8 % (22.87 - 28.46)	212 22.8% (20.00 - 25.35) .034 .13	203 22.3% (19.43 - 24.80) .020 .08
Death	n % 95 %CI [2] p value [3] P value [4]	16 1.7 % (0.88 - 2.53)	10 1.1 % (0.41 - 1.72) 0.119 .32	13 1.4 % (0.65 - 2.18) 0.311 .71
MI	n % 95 %CI [2] p value [3] P value [4]	93 9.9 % (7.99 - 11.81)	47 5.0 % (3.63 - 6.43) < .001 < .0001	48 5.3 % (3.79 - 6.67) < .001 = .0002
Repeat Revascularization	n % 95 %CI [2] p value [3] P value [4]	180 19.4 % (17.56 - 22.69)	176 19 % (16.83 - 21.89) 0.354 0.68	167 18.4 % (16.11 - 21.15) 0.260 0.45

1 For the composite, Patients were counted only once by most severe component For the analysis by component, patients may have been counted more than once. All events were counted; patients who had more than one event are listed once for each event.

2 95 % CI as per CBER Biostatistics review

3 1 sided p values calculated for time-to-event analysis using Logrank test, sig < .05, comparison to placebo, per sponsor's analysis

4 P value , calculated using Fisher's exact test, per CBER Biostatistics review

Reviewer's Note: The 6 month primary endpoint includes all revascularization procedures, and the 30 day primary endpoint includes only those that fit the definition of urgent. There is a clear cut benefit in urgent revascularizations seen in the ReoPro arms at 6 months, although there is not an appreciable difference in total procedures. See Section VB of this review for further comment.

B. SECONDARY EFFICACY ENDPOINTS

1. Death, MI or target vessel revascularization within 6 months

There was no significant difference in total repeat procedures on the target vessel among treatment arms at 6 months. The target vessel is defined as any vessel treated that was treated during the index procedure; includes urgent and non-urgent procedures within 6 months followup.

Table 12 Death, MI or target vessel revascularization within 6 months

Patients w events	Placebo n=939	ReoPro + Lo Hep n=939	ReoPro + Std Hep n=918
n	168	157	147
%	18.1 %	17.0 %	16.2 %
p value		.206	.117

* Logrank test sig < .05

2. Death, MI, or revascularization for clinically significant recurrent myocardial ischemia at 6 months

A significant difference is seen on this endpoint in the ReoPro arms compared to placebo (see Table 13 below). This endpoint is similar to the primary 30-day endpoint, although not identical. This endpoint includes urgent revascularizations for documented ischemia and repeat revascularization procedures after endpoint MI. This endpoint requires documentation of myocardial ischemia, and includes largely urgent procedures, but does not require that the ischemia be severe, as does the 30 day primary endpoint.

Table 13 Death, MI, or Revascularization for Clinically Significant Recurrent Myocardial Ischemia at 6 months

Patients w events	Placebo n=939	ReoPro + Lo Hep n=939	ReoPro + Std Hep n=918
n	138	78	76
%	14.7 %	8.4 %	8.3 %
p value		<.0001	<.0001

* Logrank test sig < .05

Reviewer's Note: An information request was sent to the sponsor regarding the lack of success in showing a difference in total revascularization procedures at 6 months. The sponsor's interpretation is that the effects of ReoPro on thrombus formation are significant enough to reduce the urgent revascularizations, even out to 6 months, but that the use of the product at the time of PTCA does not retard the progressive atherosclerosis in the coronary vessels, nor does it appear to affect the incidence of restenosis.

3. Angiographic Outcome at 6 months
These data have been submitted separately in a substudy report by the sponsor and are reviewed in another document.

4. Health Economic Analysis and Cost-Effectiveness of Treatment
This was the subject of another substudy; those data are not being submitted with this application.

V. EFFICACY RESULTS – SECONDARY AND SUBGROUP ANALYSES

A. Primary Endpoints

1. 30 Day Primary Endpoint

a. Treated Patients
There was little difference between this analysis and the primary efficacy (Intent to Treat) analysis. Only 2.4 % of patients were not treated overall, and the proportion was similar across treatment groups.

b. By Risk Classification
Risk was assessed twice in this study, at the time of randomization, and following the index procedure when the detailed lesion morphology classification was completed. This study sought to extend the demonstration of efficacy seen in the EPIC trial to include patients at lower risk for acute cardiac ischemic complications following the procedure. Subset analyses by risk classification were not explicitly planned in the protocol, however. The subset analyses show efficacy associated with Abciximab in the higher risk subset of patients, whether classified by the at-randomization or the CRF assessment. The low-risk subset as identified at randomization shows efficacy of Abciximab. The low risk subset as identified by the CRF assessment shows no trends toward efficacy (Table 14).

There was a small number of patients (25) whose clinical status was recorded incorrectly at randomization, and was corrected on the CRFs, resulted in reclassification of those patients by risk status. Table 15 (see next page) shows the primary endpoint event rates by the as randomized risk status, incorporating the changed risk status of the 25 patients whose status changed for clinical reasons. There is no substantial alteration in event rates by treatment arm when these changes are incorporated.

Table 14 Primary Endpoint Events At 30 Days By Randomized And By CRF Risk Classification

	Placebo n=939	ReoPro Lo Hep n=935	ReoPro Std Hep n=918
RANDOMIZED CLASSIFICATION			
High Risk Patients	602	602	590
Events	78	40	33
%	13 %	6.6 %	5.6 %
p value[1]		< .001	< .001
Low Risk Patients	337	333	328
Events	31	8	16
%	9.2 %	2.4 %	4.9 %
p value[1]		< .001	< .001
PER CRF CLASSIFICATION			
High Risk Patients	748	738	732
Events	100	39	40
%	13.4 %	5.3 %	5.5 %
p value[1]		< .001	< .001
Low Risk Patients	176	186	175
Events	8	3	9
%	4.6 %	3.2 %	5.1 %
p value[1]		NS	NS

Source: Datasets

1 p value computed using Chi Square test as per CBER Biostatistics Review

Table 15 Primary 30 Day Endpoint by Randomized Risk Status after patients whose risk status changed for clinical reasons were incorporated

Patients with Death, MI or Urgent Revascularization	Placebo n=939	ReoPro Lo Hep n=935	ReoPro Std Hep n=918
High Risk Patients	611 78 12.8 %	609 40 6.6 %	599 33 5.5 %
Low Risk Patients	328 31 9.5 %	326 8 2.5 %	319 16 5.0 %

e. By Component by Subgroup

(i) Age, gender and weight

Men less than 65 years were the largest subgroup in the trial, and substantial reductions in the primary 30-day endpoint is seen in this group (see Figure 2 below; hazard ratios are shown comparing the placebo arm to the combined Abciximab arms). Substantial reductions are also seen in women < 65 years, but there were fewer patients in this subgroup. For patients over age 65, there is a trend toward reduction of events that is of lesser magnitude in women, and is not statistically significant in either women or men. Again, there were far fewer patients in these subgroups.

The ReoPro bolus and the heparin bolus and infusions were weight-adjusted in this trial. Analysis of subgroups by body weight < 75 kg, 75 - 90 kg, and > 90 kg shows a consistent reduction in primary endpoint events in all these groups, as is shown in Figure 2.

Of interest, the largest subgroup in the trial included patients weighing ≥ 90 kg. The Abciximab infusion was not weight adjusted for patients weighing over 80 kg. The improved primary endpoint rates in the ReoPro groups were seen consistently across patients weighing ≥ 80 kg also.

Figure 2 Hazard Ratios for Primary 30 Day Endpoint by Age, Gender, and Body Weight

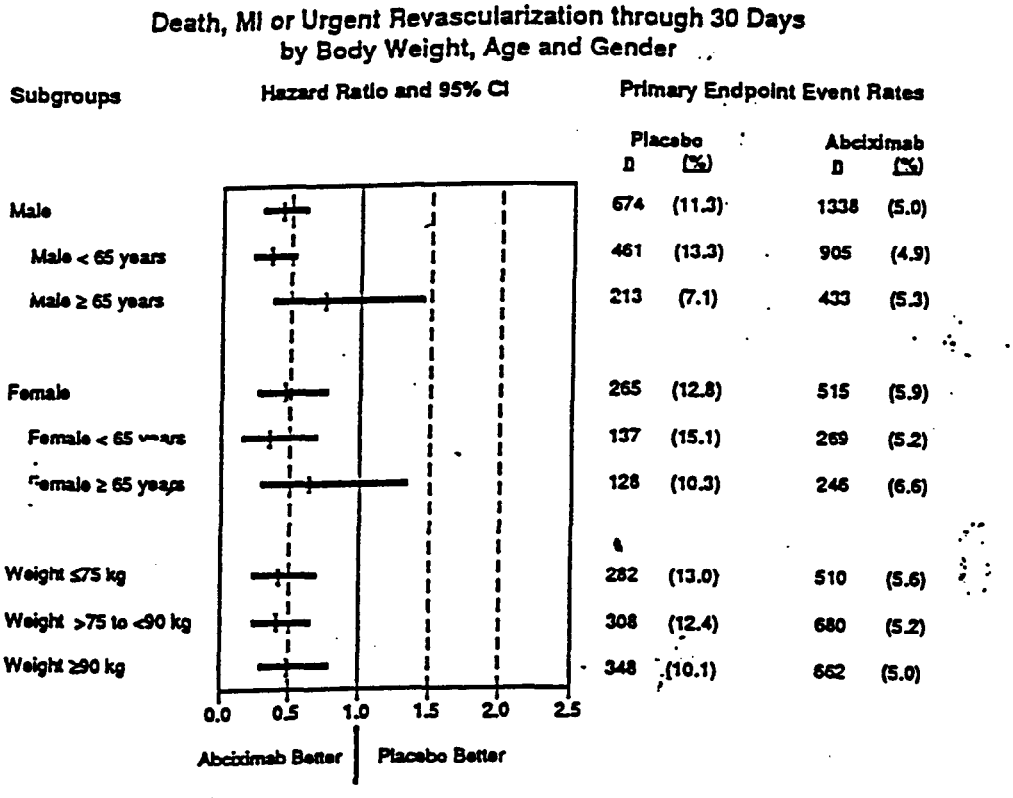

Figure 2 Hazard Ratios and the 95% Confidence Intervals (CI) for Death, MI or Urgent Revascularization by Gender, Age and Body Weight. The number of patients and the event rates are shown on the right side for each clinical event according to treatment group. Hazard ratios <1 indicate abciximab is better and hazard ratios >1 indicate that placebo is better.

(ii) History of Diabetes and prior Myocardial Infarction

The presence of diabetes and recent myocardial infarction in a patient's history may be factors which significantly predict risk of ischemic events. Patients with a history of diabetes mellitus comprised 22% of the patients in the study. Primary endpoint rates appear significantly reduced in both patients with and without a prior history of diabetes in ReoPro arms compared to placebo. (See Figure 3)

Forty-eight percent of patients in the trial had a history of prior MI. Endpoint events are consistently reduced in both patients with and without prior MI, and among patients with prior MI, whether the MI occurred at any point, 7 days or more prior. Patients with a history of MI within the prior 7 days had a somewhat higher event rate in the placebo arm (14.7 %), but demonstrated significant 30-day endpoint reductions in both ReoPro arms. Patients with MI between 8-30 days prior were the smallest subgroup; nonetheless, a trend to reduction of primary endpoints was also seen in these patients. (See Figure 3)

Figure 3 Primary Endpoint at 30 Days By Clinical Risk Factors

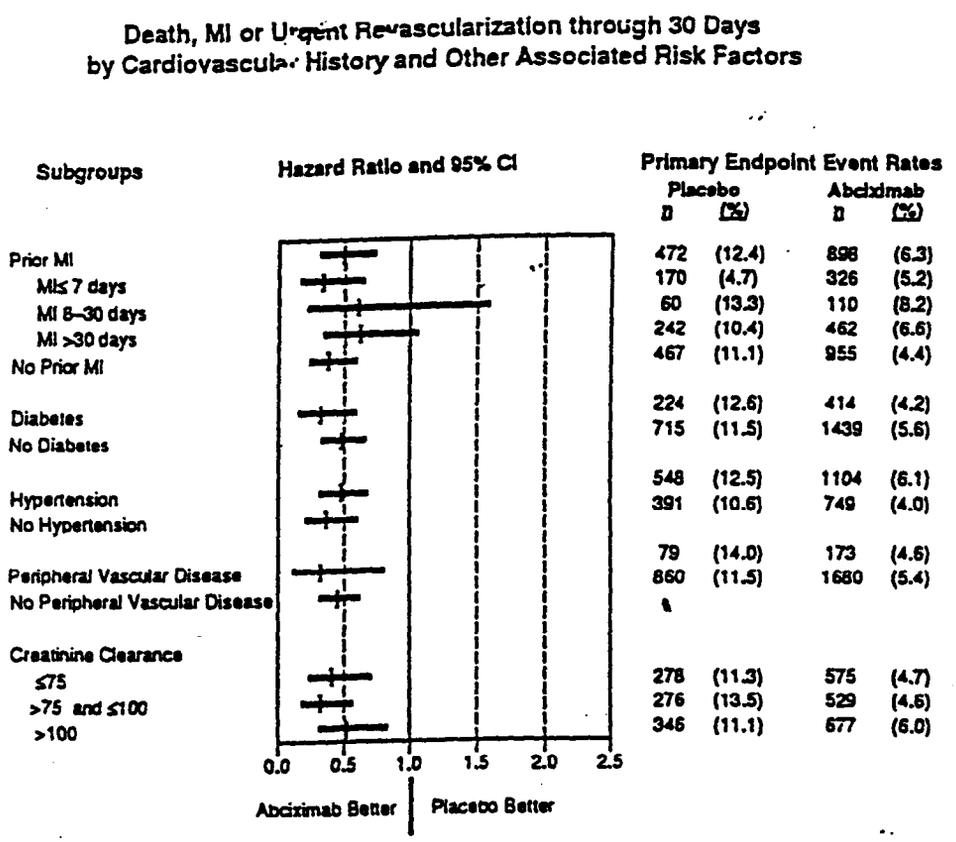

Figure 3 Hazard Ratios and the 95% Confidence Intervals (CI) for Death, MI or Urgent Revascularization by Cardiovascular History and Risk Factors. The number of patients and the event rates are shown on the right side for each clinical event according to treatment group. Hazard ratios <1 indicate abciximab is better and hazard ratios >1 indicate that placebo is better.

d. Type of MI

Clear trends toward reduction of all types of MI in the ReoPro treated patients are seen, particularly for large non-Q wave MI, which comprised two-thirds of all MI during the 30 day follow up. The number of Q wave MI is reduced in the ReoPro treated arms, but is too small to reach statistical significance (see Table 16).

Table 16 Patients With Endpoint MI During 30 Day Followup

	Placebo n=939	ReoPro Lo Hep n=935	ReoPro Std Hep n=918
All MI n %	81 8.6 %	34 3.6 %	35 3.8 %
Q Wave MI n %	7 0.7 %	4 0.4 %	4 0.4 %
Large non Q[1] n %	56 5.9 %	19 2.0 %	23 2.5 %
Small non Q n %	18 1.9 %	11 1.2 %	8 0.9 %

1 Includes during (95) and after (3, all placebo) index hospitalization

Reviewer's Comment: The benefit was seen more in large non Q wave MI in EPILOG, as has been seen in the EPIC trial. Eighty percent of the MIs occurring during the study period in EPIC were non Q wave; 90% were non Q wave in EPILOG. Both Q Wave and NonQ wave MIs were reduced in EPIC with ReoPro treatment.

e. Cause of Death

At the 30-day assessment the number of deaths was small in all arms. There were more cardiac deaths in the placebo arm than in the ReoPro arms combined. Three deaths were due to ICH; all in the ReoPro arms. More were due to definite or observed MI in the placebo patients (see Table 17).

Table 17 Cause of Death at 30 Days

	Placebo n=939	ReoPro Lo Hep n=935	ReoPro Std Hep n=918
Cardiac	5	2	2
Intracerebral Hemorrhage	0	1	2
Unknown	2	0	0
Total	7	3	2

f. Primary Endpoint by Indication for PTCA

Consistent results were seen for patients with unstable angina, recent MI (defined as MI occurring between 24 hours and 7 days prior) and for stable angina and other indications (includes chronic stable angina or a positive functional test as the indication for the procedure) on both death and MI and death, MI and urgent revascularization at 30 days. Primary endpoint rates were significantly reduced for Abciximab treated patients compared to placebo in both patients with unstable angina and stable angina or positive functional tests. Results trended favorably for patients with recent MI (see Table 18).

Although there were a modestly higher percentage of patients in the placebo arm with unstable angina compared to the percentage in the Abciximab treated arms (see Table 1, earlier), as the event rates were comparable for patients with unstable angina, recent MI, and stable angina/other indications, this does not affect the overall endpoint results.

Table 18 Composite Primary Endpoint at 30 Days by Indication for PTCA

Deaths, MI, or Urgent Revascularizations	Placebo n=939	ReoPro Lo Hep n=935	ReoPro Std Hep n=918
Patients with Unstable Angina Events %	474 57 12.2 %	434 21 4.8 %	420 21 5.0 %
Patients with Recent MI Events %	189 21 11.1 %	200 15 7.5 %	190 8 4.2 %
Patients with Chronic Stable Angina and Positive Functional Tests Events %	276 31 11.3 %	301 12 4.1 %	308 20 4.1 %

g. Primary Endpoint at 30 days by type of device used

Most patients were treated with balloon angioplasty only. Event rates were higher in patients treated with STENT and rotational or other atherectomy, but consistent trends were seen in reduction of endpoint rates in the Abciximab arms compared to placebo. Table 19 presents a listing of event rates by type of device used in the index procedure.

Table 19 Composite Primary Endpoint at 30 Days by Type of Device Used

Deaths, MI, or Urgent Revascularizations	Placebo n=939	ReoPro Lo Hep n=935	ReoPro Std Hep n=918
Patients with Balloon Only Events %	705 48 6.9 %	751 20 2.7 %	702 21 3.0 %
Patients with STENTs Events %	144 28 19.5%	100 7 7.0 %	138 10 7.2 %
Patients with Rotational or Other Atherectomy Events %	57 10 19.2 %	56 4 8.2 %	56 4 8.2 %

h. Primary Endpoint at 30 Days by Procedural Factors and Lesion Characteristics
The sponsor has provided an exploratory analysis defining hazard ratios for subgroups of patients by certain procedural factors and by complexity of the lesion as designated by the investigators at randomization. Clear benefit is demonstrated for patients with one or more than one segment treated, for patients with and without prior PTCA, and for patients with and without thrombus in the lesion to be treated. Event rates in the placebo arm are low for patients with Type A lesions, particularly Type A de novo lesions, and for patients with only 1 Type B characteristic. For those subgroups, there does not appear to be a demonstrable benefit from the use of Abciximab in this sample. (See Figure 4).

Death, MI or Urgent Revascularization through 30 Days
by Procedural Factors Influencing Clinical Outcome

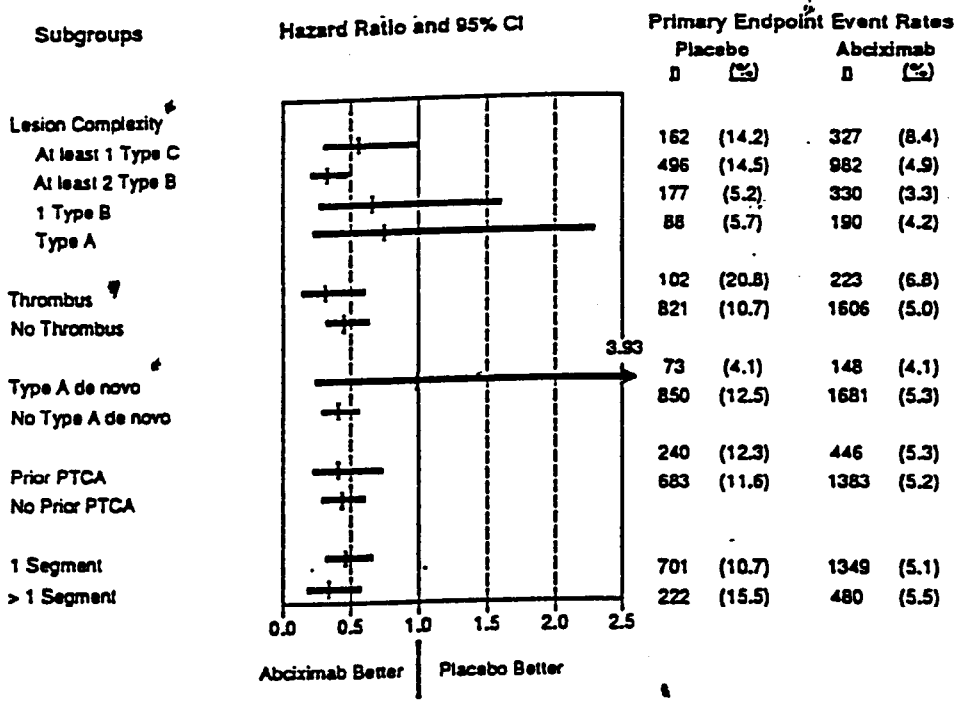

Figure .4 Hazard Ratios and the 95% Confidence Intervals (CI) for Death, MI or Urgent Revascularization by Procedural Factors Influencing Clinical Outcome. The number of patients and the event rates are shown on the right side for each clinical event according to treatment group. Hazard ratios <1 indicate abciximab is better and hazard ratios >1 indicate that placebo is better. * CRF data

i. Primary Endpoint at 30 days by Study Site

Results are fairly consistent among sites of large enough size to permit comparison. Table 20a shows event rates by whether sites were academic or non-academic medical centers. Of interest is that placebo event rates were lower at academic medical centers, while the rates in the Abciximab treated patients were similar at both academic and non-academic centers.

Reviewer Comment: It may be that the academic centers enrolled a higher proportion of patients with very low risk status,or that ancillary care at the academic sites contributed significantly to lower event rates.

Table 20a Primary Endpoint at 30 days by Academic and Non-Academic Centers

Deaths, MI, or Urgent Revascularizations	Placebo n=938	ReoPro Lo Hep n=935	ReoPro Std Hep n=918
Academic Centers n	276	272	266
Events	24	12	15
%	8.7 %	4.4 %	5.6 %
Non-Academic Centers n	662	663	652
Events	85	36	34
%	12.8 %	5.4 %	5.2 %

The proportion of patients designated as high and low risk by the as randomized classification and the primary endpoint event rates for each subgroup, by academic and nonacademic sites, are shown in Table 20b. The placebo event rate for the patients identified as low risk at the academic centers is extremely low, while those identified as low risk at the nonacademic centers have an event rate more comparable to the overall rate.

Table 20b Primary Endpoint by Risk Status at Randomization and by Academic and NonAcademic Centers

Deaths, MI, or Urgent Revascularizations	Placebo LOW RISK n = 337	Placebo HIGH RISK n = 601	ReoProLoHep LOW RISK n = 333	ReoProLoHep HIGH RISK n = 602	ReoProStdHep LOW RISK n = 338	ReoProStdHep HIGH RISK n = 590
Academic Centers n	100	176	99	173	93	173
Events	2	22	1	11	4	11
%	2.0 %	12.5 %	1.0 %	6.4 %	4.3 %	6.4 %
Non-Academic Centers n	237	425	234	429	235	417
Events	29	56	7	29	12	22
%	12.2 %	13.2 %	3.0 %	6.8 %	5.1 %	5.3 %

The same analysis by CRF risk classification (made retrospectively, after the procedure) is shown in Table 21. By this classification, the placebo event rate in the patients identified as low risk is consistently lower than that for the patients identified as high risk at both academic and nonacademic centers.

Table 21 Primary Endpoint by Risk Status per CRF and by Academic and NonAcademic Centers

Deaths, MI, or Urgent Revascularizations	Placebo LOW RISK n = 176	Placebo HIGH RISK n = 747	ReoProLo Hep LOW RISK n = 186	ReoProLoHep HIGH RISK n = 738	ReoProStdHep LOW RISK n = 211	ReoProStdHep HIGH RISK n = 700
Academic Centers n Events %	64 1 1.6 %	207 23 11.1 %	69 2 2.9 %	200 10 5.0 %	67 2 2.9 %	205 12 5.8 %
Non-Academic Centers n Events %	112 7 6.3 %	540 77 14.3 %	117 4 3.4 %	538 29 5.4 %	118 6 5.1 %	527 28 5.3 %

Reviewer Comment: The event rate for low risk patients in the placebo group as identified at academic centers by either randomization or CRF appears similar, and substantially lower than the overall event rate. The placebo event rate for low risk patients at non-academic centers appears as high at randomization as the rate for the high risk patients; it is substantially lower by the CRF assessment. If event rates are used as an indicator of risk, then perhaps academic investigators predicted risk status more accurately at randomization than did investigators at non-academic centers. However, the procedural outcome, and in some cases the patients's clinical course, were known at the time of CRF completion, which may have biased that assessment.

2. 6 Month Primary Endpoint

a. Deaths by Cause @ 6 months

There were a total of 39 deaths over the 6 month followup period in the trial. There were 21 cardiac deaths, distributed evenly (7 each) per arm.

There were 3 deaths attributed to hemorrhagic stroke, none in the placebo arm, 1 in the ReoPro Low dose arm and 2 in the Abciximab Standard Dose Heparin arm. In addition, the ReoPro Std Dose arm had 1 other vascular death.

Non-cardiac medical deaths occurred infrequently, 1 per arm. There was one non-cardiac trauma-related death, in the placebo arm. There were 7 "unknown" causes of death in the placebo arm; patients who died after hospital discharge, for whom the cause of death was undetermined. There were a total of 3 unknown causes of death in the Abciximab arms, 1 in the Low Dose and 2 in the Standard Dose Heparin arms.

b. By Risk Classification

When the 6 month primary endpoint is examined by randomized risk classification, the results are variable. There are significantly less events in high risk patients in the ReoAPro Standard Dose Heaprin arm, and a trend toward less events in low risk patients in th eReoPro Low Dose Heparin arm by this classification (see upper portion of table 22). This endpoint includes any revascularization procedures.

The benefit seen on the primary 30 day endpoint in Abciximab treated patients is seen to be sustained at 6 months in both high and low risk patients, as they were identified at randomization. This endpoint includes death, MI, and urgent revascularizations (see lower portion of table 22).

Table 22 Death, MI, Or Repeat Revascularization During 6 Month Follow-Up By Risk Classification At Randomization

Death, MI or Repeat Revascularization	Placebo n=939	ReoPro Lo Hep n=935	ReoPro Std Hep n=918
High Risk Patients	602	602	590
Events	166	153	132
%	27.7 %	25.4 %	22.6 %
p value		0.43	0.04
Low Risk Patients	337	333	328
Events	75	59	71
%	22.4 %	17.8 %	21.7 %
p value		0.15	0.85
Death, MI, or Urgent Revascularization			
High Risk Patients	602	602	590
Events	98	61	53
%	16.3 %	10.2 %	9.0 %
p value		.002	.0002
Low Risk Patients	337	333	328
Events	40	17	23
%	11.9 %	5.1 %	7.0 %
p value		.002	.035

1 Event rates from Kaplan/Meier/ Logrank test time to event analysis

By the CRF risk classification, there is evidence of benefit in the patients assessed as high risk on both the 6 month primary endpoint including all revascularization procedures, and the 6 month composite including only urgent interventions, but the results for the low risk patients do not show a difference (see Table 23).

Table 23 Death, MI, Or Repeat Revascularization During 6 Month Follow-Up By CRF Risk Classification

Death, MI or Repeat Revascularization	Placebo n=939	ReoPro Lo Hep n=935	ReoPro Std Hep n=918
High Risk Patients Events % p value	748 207 27.7 %	738 174 23.6% 0.08	732 167 22.8 % 0.04
Low Risk Patients Events % p value	176 31 17.6 %	186 33 17.7 % 1.0	175 34 19.4 % 0.7
Death, MI, or Urgent Revascularization			
High Risk Patients Events % p value	748 124 16.6 %	738 63 8.5 % < .0001	732 62 8.5 < .0001
Low Risk Patients Events % p value	176 13 7.4 %	186 12 6.5 % 0.8	175 14 8.0 0.8

1 Event rates from Kaplan/Meier/ Logrank test time to event analysis
2 2 sided P values based on Fisher exact test, per CBER Biostat analysis

c. By Type of MI

Non Q wave MI were reduced by more than half in each Abciximab treated arm compared to placebo. There was not a significant reduction in Q wave MIs, but the numbers of events were small (Table 24).

Table 24 Patients With Endpoint MI During 6 Month Followup *

Events	Total n=2792	Placebo n=939	ReoPro Lo Hep n=935	ReoPro Std Hep n=918
All MI %	188	93 9.9 %	47 5.0 %	48 5.3 %
Q Wave %	40	15 1.6 %	12 1.3 %	13 1.4 %
All non Q %	151	79 8.4%	36 3.9 %	36 3.9 %

*Kaplan/Meier/ Logrank test; some patients counted in both categories

B. Exploratory Analyses on Secondary Endpoints

1. Death, MI and repeat revascularization at 30 days

A significant difference in all repeat revascularizations at 30 days (that is the 6 month primary endpoint at the 30 day timepoint) was seen in Abciximab treated arms compared to placebo. These trends were also seen in endpoints with target vessel procedures and repeat revascularizations for clinically significant ischemia, as shown in Table 25 below.

Table 25 Death, MI And Revascularization Procedures At 30 Days

Patients w Death, MI and...		Total	Placebo (n=939)	Reo Lo Hep* (n=935)	Reo Std Dose* (n=918)
Repeat Revascularization	n	277	129	74	74
	%		13.9 %	8.0 %	8.2 %
Target Vessel Revascularzn	n	250	125	61	64
	%		13.4 %	6.7%	7.0 %
Revasc for Clin Sig Ischemia	n	236	116	60	60
	%		12.5 %	6.5 %	6.6 %

* Logrank test, all sig @ <.001 +Patients may be counted in more than one analysis

2. All revascularizations, urgent and non-urgent and CABG at 6 months

The ReoPro arms showed a marked decrease in urgent procedures; however, as urgent procedures only comprised one-fourth of total revascularization procedures done over the 6 month period, there was no significant difference in total repeat procedures among treatment arms (see table 26). Most revascularization procedures were non-urgent. Non-urgent procedures were actually slightly increased in the ReoPro Lo Dose arm compared to the placebo arm.

There is a small trend toward less target vessel revascularizations and revascularization procedures for clinically significant ischemia in the Abciximab treated patients at 6 months, but no significant difference was seen on these rates among Abciximab treated patients compared to placebo treated patients (Table 26 also).

Reviewer's Note: The factors responsible for the "catching up" of non-urgent revascularization rates in the Abciximab treated arms are not clear. The sponsor has suggested this may be due to the inability of the Abciximab infusion for a 12-hour period to retard the natural progression of the underlying atherosclerotic disease in both the treated vessel and other vessels.

Table 26 Patients With Revascularization Procedures at 6 Months

Patients w events	Total (n=2792)	Placebo (n=939)	Reo Lo Hep(n=935)	Reo Std Hep(n=918)
All Repeat Revascularizations n % 95 % CI p value[2] (excludes staged procedures)[1]	523	180 19.4 %	176 19.0 % 0.354	167 18.4 % 0.260
Urgent Revascularization n % 95 % CI p value	124	63 6.7 % (5.11 - 8.31)	29 3.1 % (1.99 - 4.21) <.001 (= .0004)	32 3.5 % (2.30 - 4.67) <.001 (= .0021)
Non-Urgent Revascularization n % p value	421	127 13.8 % (11.34 - 15.71)	155 16.7 % 0.037	139 15.4 % 0.165
Target vessel Revascularization n % p value	472	168 18.1 %	157 17.0 % 0.206	147 16.2 % 0.117
Revasc for Clin Signif Ischemia n % p value	460	159 17.1 %	152 16.4 % 0.296	149 16.5 % 0.301

* A total of 17 procedures were staged, 9 placebo, 5 RLD and 8 RSD

2 p value from chi square test per CBER Bostatistics review

Similarly, urgent CABG rates occurred at markedly lower rates in Abciximab treated patients (see Table 27). Non-urgent CABG rates were not different among treatment arms, however.

Table 27 Patients Who Had CABG During 6 Month Follow-Up[1]

	Placebo N = 939	Reo Lo Hep N = 918	Reo Std Hep N = 935
Patients w CABG n % P value[1]	 70 7.5 %	 56 6.0 % 0.094	 56 6.2 % 0.119
Urgent CABG n % p value[1]	 22 2.4 %	 6 0.6 % 0.001	 9 1.0 % 0.011
Non-Urgent CABG n % p value[1]	 48 5.2 %	 50 5.4 % 0.429	 47 5.2 % 0.491

1 Rates and p values from Log-Rank Time to Event Analysis

Reviewer's Note: Again, this differential effect on urgent and non-urgent procedures may be due to progression of atherosclerosis despite the effect on thrombosis in patients treated with Abciximab which reduces the number of urgent procedures performed in those patients.

VI. SAFETY RESULTS

A. Prespecified Primary Analyses

The two primary safety endpoints prespecified were:

1) Death and hemorrhagic stroke incidence over the 6 month duration of the trial, and

2) Major non CABG associated bleeding rates during hospitalization or within the first 7 days of hospitalization

1. Death and hemorrhagic stroke incidence over the 6 month duration of the trial
There was no significant difference in the incidence of death and hemorrhagic stroke between treatment arms. A small number of events occurred in each arm. Table 28 shows rates of death and hemorrhagic stroke at 6 months and at 30 days in all treatment arms.

Table 28 Death and Hemorrhagic Stroke at 6 Months and at 30 Days

	Placebo N = 939	Reo Lo Hep N = 935	Reo Std Hep N = 918
Death and Hem Stroke @ 6 mo	16	11	15
Death	16	10	13
Hem Stroke	0	1	2
Death & Hem Stroke @ 30 days	7	4	5
Death	7	3	4
Hem Stroke	0	1	1

* Note: this table only includes hemorrhagic stroke. There were 2 intracranial bleeds (one subdural and one both subdural and subarachnoid) in patients in the ReoPro + Std Dose Heparin arm occurring at 10 hours and at 8 hours, which are not listed here). Additionally, 1 patient in the ReoPro Std Dose arm had a hemorrhagic stroke (cerebellar lacune) at 18 days, which was not reported until after the 30 day database lock.

2. Major non CABG associated bleeding rates during hospitalization or within the first 7 days of hospitalization

Major non CABG bleeding rates were not significantly different in the ReoPro Low Dose Heparin arm from placebo, (10 in each arm) but the rate in the ReoPro Standard Dose Heparin arm was almost doubled (17), although not statistically significant ($p = 0.18$). Minor non CABG bleeding was significantly increased in the ReoPro Standard Dose Heparin arm compared to placebo.

B. All Other Prespecified Safety Analyses

1. Bleeding

a) Major and minor overall (this includes both bleeding associated with and not associated with CABG) There was no significant difference in the proportion of major bleeds among arms. There was a clear trend to less major bleeding in the ReoPro Low Dose arm compared to placebo, though it was not statistically significant. ReoPro with Standard Dose heparin had a few more major bleeds than the placebo arm (standard dose heparin alone); this difference was not significant.

Minor bleeds are significantly increased (doubled) in the ReoPro with-Standard Dose heparin arm, however. It should be noted that what is termed "minor" bleeding in this trial actually represents a substantial loss of blood. No significant difference appears between minor bleeding in the ReoPro Low Dose and placebo arms. The number and proportion of patients with insignificant or no bleeding is highest in the ReoPro with Low Dose Heparin arm.

Table 29 Major And Minor Bleeding Overall (includes CABG related bleeding)

Patients w events	Placebo N = 939	Reo + Lo Hep N = 918	Reo + Std Hep N = 935
Major or Minor Bleeding n %	 64 6.8 %	 56 6.0 %	 100 10.9 %
Major bleeding n %	 29 3.1 %	 19 2.0 %	 32 3.5 %
Minor bleeding n %	 35 3.7 %	 37 4.0 %	 68 7.4 %
Insig or No Bleeding n %	 834 (189 + 645)# 88.8 % (20 + 68)#	 848 (281 + 567)# 90.7 % (30 + 60)#	 780 (288 + 492)# 85.0 % (31 + 53)#
Patients not eval'd	41 4.4 %	31 3.3 %	38 4.1 %

Numbers in parens indicate the number and percentages of patients with insignificant + no bleeding)--from CBER Biostatistics review

Reviewer's Note: In the EPIC trial, of 2099 patients, 222 had major bleeds--99 in the bolus and infusion group (14 %), 77 in Bolus only, and 46 in placebo (6.6 %). The risk was increased in patients ≥ 65 yrs, weight < 75 kg, acute MI w/in 12 hrs prior to PTCA, prolonged or failed PTCA, history of GI Bleed. Bleeding rates in all arms in the EPILOG trial were remarkably reduced compared to those in the EPIC trial, probably owing to the combination of factors that were changed in the EPILOG trial; e.g., the weight adjustment of heparin and ReoPro dosing, the decreased duration of heparin treatment, and the more stringent requirements for access site care, in addition to the use of the low dose heparin in that treatment arm. Heparin weight adjustment, duration and dose appear to have been the most important factors.

(b) By Subgroup

No significant differences were seen in bleeds by weight or gender or age. See discussion in next section of non - CABG associated bleeding by these variables.

2. CABG and Non-CABG Bleeding

(a) Overall

The major non CABG bleeds in the ReoPro low dose heparin arm were equal in number and percentage to those in the placebo arm. As noted under A. above, there were a greater number of major non CABG bleeds in the ReoPro Std Dose heparin arm (nearly double the placebo rate), but the numbers were too small to reach statistical significance.

Minor non CABG bleeds were similar in the ReoPro Low Dose heparin arm to the placebo rate, and were significantly increased to more than double the placebo rate in the ReoPro Standard Dose heparin arm. (See Table 30 below)

Table 30 Non CABG Bleeding

Patients with events	Placebo n = 939	Reo Lo Hep n = 935	Reo Std Dose n = 918
Significant Bleeding	42 4.5 %	47 5.1 %	87 9.5 %
Major bleeds n % P value	10 1.1 %	10 1.1 %	17 1.9 % 0.178
Minor bleeds n % p value	32 3.4 %	37 4.0 %	70 7.6 % < 0.001

Reviewer's Note: Exploratory analyses revealed a number of patients in all arms who had "insignificant" bleeds that did not meet the criteria for a minor or major bleed). When these are added, the percentage of patients with any bleeding increases to 25 % placebo, 35 % ReoPro Lo Dose Heparin, and 41 % in the ReoPro Standard Dose Heparin arm. (Source: CBER Biostatistics Review)

Table 31 presents the bleeding associated with CABG by treatment arm. This bleeding accounted for over half of the major bleeding in the trial.

Table 31 Bleeding Associated With CABG

Patients w events	Placebo	Reo Lo Hep	Reo Std Dose
Patients w/ CABG	26	11	16
Any Bleeding	23 88 %	11 100 %	16 100 %
Major bleeds n %	19 73 %	9 82 %	16 100 %
Minor bleeds n %	4 15 %	2 18%	0 0%

Reviewer's Note: All patients who had CABG in the ReoPro arms had some form of significant bleeding, as did nearly all patients in the placebo arm. Note that all CABG patients in the ReoPro Standard Dose arm had Major bleeds.

Most patients in the EPIC trial who underwent CABG (33 in each, placebo & bolus - infusion arms) had major bleeding (73 % placebo, 78 % bolus - infusion). These results are not markedly different. There were fewer patients going to CABG in the ReoPro treated arms than in the placebo arm however, in both EPIC and EPILOG.

3. Transfusions

The number of patients receiving transfusion of PRBCs or whole blood was small in the EPILOG trial. Less patients in the Abciximab Low Dose Heparin arm received transfusions compared to either placebo or Abciximab plus Std Dose Heparin (patients in the placebo arm also received standard dose heparin (see Table 32).

Table 32 Transfusions

	Placebo (n = 939)	ReoPro Lo Dose (n = 935)	ReoPro Std Dose (n = 918)
PRBCs or Whole Blood	37	18	30
Non - CABG	10	6	7
Platelets	10	8	15
Non - CABG	1	0	1

The most common reasons cited for transfusion was preparation of the patient for CABG or a decrease in Hemoglobin or Hematocrit. Platelet transfusions were also uncommon, particularly among patients not undergoing CABG.

(b) Bleeding by Age, Gender, and Body Weight

No differences of importance were seen in rates of major bleeding in either women or in older patients in the Abciximab and Low Dose Heparin arm compared to placebo.

Reviewer's Note: Bleeding rates in women and in patients over 65 years of age were substantially higher than among other age and gender groups among patients in all arms in the EPIC trial.

There were higher rates of major non-CABG bleeds among women over 65 years in the arms treated with Standard Dose Heparin, but the numbers of patients in this subgroup were relatively small. A notable, but not significant difference was seen in both women and men ≥ 65 years in the ReoPro Standard Dose Heparin arm. Table 33 presents major non-CABG associated bleeding by gender and age.

No significant differences were seen in any weight subgroups among the treatment arms in major non-CABG bleeding (see Tables 34 and 35).

Table 33 Major Non CABG Bleeds By Gender And Age

Patients w major bleeds	Placebo	Reo Lo Hep	Reo Std Dose
Men < 65 yr n % p value[1]	461 3 0.7 %	465 4 0.9 % 1.00	440 4 0.9 % 0.720
Men ≥ 65 yr n % p value[1]	213 2 0.9 %	203 2 1.0 % 1.00	230 6 2.6 % 0.288
Women < 65 yr n % p value	137 2 1.5 %	141 3 2.1 % 1.00	128 1 0.8 % 1.00
Women ≥ 65 yr n % p value[1]	128 3 2.3 %	126 1 0.8 % 0.622	120 6 5.0 % 0.321

*1 p value is compared to placebo; based on log rank time to event analysis

Table 34 Major Non CABG Bleeds By Body Weight

Patients w major bleeds	Total	Placebo	Reo Lo Hep	Reo Std Dose
Patients ≤ 75 kg n % p value1	792 11 1.4 %	282 3 1.1 %	272 2 0.7 % 1.00	238 6 2.5 % 0.313
Patients > 75 to < 90 kg n % p value[1]	988 15 1.5 %	308 3 1.0%	326 5 1.5 % 0.726	354 7 2.0 % 0.352
Patients ≥ 90 kg n % p value[1]	1010 11 1.1 %	348 4 1.1 %	336 3 0.9 % 1.00	326 4 1.2 % 1.00
Wgt unknown	2	1	1	0

1 Log rank time to event analysis sig <.05

Patients over 80 kg received a fixed dose regimen of Abciximab. When data are analyzed by weight subgroup using the 80-kg cutoff, no significant differences in the rates on bleeding are seen when patients < 80 kg are compared to patients ≥ 80 kg. (See table 35 below).

Reviewers' Note: All patients in the trial had weight adjusted heparin doses. Over half the patients in the trial (1,707 patients) fell into the group weighing ≥ 80 kg, and received a fixed dose of 10 ug/min Abciximab.

Table 35 Major Non CABG Bleeds By Body Weight

Patients w major bleeds	Placebo n = 939	Reo Lo Hep n = 935	Reo Std Dose Hep n = 918
Patients < 80 kg n %	378 3 0.8 %	367 5 1.3 %	338 7 2.1 %
Patients ≥ 80 kg n %	560 7 1.3%	567 5 0.88 %	580 10 1.7 %

4. Timing of Bleeds

(a) The CEC analyzed bleeding by time of occurrence. There were more cases of major bleeding occurring during the period from baseline to 36 hours in the Abciximab Standard Dose Heparin arm. More of the minor bleeding in all arms occurred within the first 36 hours, as well, more so in both of the Abciximab arms than placebo. More patients in the placebo arm were receiving heparin for a longer time period, suggesting a correlation of later bleeding to extended heparin usage.

(b) Hemoglobin changes and transfusions within 48 hrs of end of study agent in patients undergoing CABG were greater in patients treated with the standard dose heparin regimen than in the Abciximab-low dose heparin arm. The Abciximab treated patients who subsequently went to CABG were usually treated with platelet transfusions to reverse the antiplatelet effects prior to surgery. Heparin, however, was continued. Bleeding complications were frequent in these patients. There were more transfusions in Placebo and Abciximab Standard Dose Heparin patients, suggesting a stronger relationship of bleeding during this time period to heparin usage.

Reviewer's Note: It is difficult to identify with certainty which of the agents is more responsible for non-CABG related bleeding complications by assessment of timing during the period beyond administration of the study agent. The effects of Abciximab may be present on platelets for up to 15 days after administration, and the patients are also still being treated with aspirin.

5. Bleeding By Location

The most common location of both major and minor bleeding events was at the femoral arterial access site. Approximately 70 % of major bleeding occurred at the femoral access site in all treatment arms, as did 62 to 83 % of minor bleeding. More patients in the ReoPro treated arms had minor arterial access site bleeding only than did patients in the placebo + Std dose heparin (over 80 % compared to 60 %). More patients in the placebo + Std dose heparin and the ReoPro + Std Dose Heparin arms had either major or minor bleeding at sites other than the arterial access site, including GI and GU bleeding, and a single case of major retroperitoneal bleeding occurred in a placebo patient.

See Table 36 for a listing of major and minor bleeds by location.

Reviewer's Note: The largest proportion of major bleeding occurred at the femoral and other arterial access sites in patients in the EPIC trial also. Compared to the EPIC trial, there were many fewer sheath site and GI, GU and retroperitoneal bleeds in the patients in the EPILOG trial in all treatment arms. Major GI, GU, sheath site and retroperitoneal bleeding rates among Abciximab treated patients in EPIC were also substantially increased compared to placebo treated patients.

Table 36 Major And Minor Non CABG Bleeds By Location

Location	Placebo n = 939		Reo Lo Hep n = 935		Reo Std Dose Hep n = 918	
	Major	Minor	Major	Minor	Major	Minor
All Non CABG Bleeds	10	32	10	37	17	70
Femoral Access Site	7	20	7	31	12	58
Other Arterial Site	3	2	3	2	0	0
GI	1	6	2	1	1	9
GU	1	4	0	5	2	9
Retroperitoneal	1	0	0	0	0	2
Intracranial	0	-	1	-	2	-
Other*	1	1	0	2	5	5
Dec Hb or Hct only	1	9	2	6	5	20

* Other includes eye, ear, nose, throat, pulmonary and pericardial sites

6. Stroke and ICH by Timing of Occurrence

The incidence of stroke and intracranial bleeding was not statistically different among treatment arms, although more events occurred in the Abciximab treated arms (see table 37). Events occurring during the index hospitalization or within the first 14 days after randomization are the most relevant to treatment with Abciximab, as the agent is expected to be cleared from the platelets by the end of that period. (see Table 38).

Reviewer Note:

Rates of intracerebral hemorrhage and nonhemorrhagic stroke in the EPIC and CAPTURE trials were not significantly different between Abciximab and placebo treated patients; the integrated data shows events in 7 of 2,225 (0.31 %) placebo patients and 10 of 3,112 (0.32 %) Abciximab-treated patients across all 3 trials in the 30 day period after randomization. The rates of ICH alone were 0.13 % in placebo patients and 0.19 % in Abciximab patients.

This study was not powered to adequately detect a difference in events of such low frequency, and a real difference can not be ruled out entirely on the basis of these data. Further examination of the clinical histories of patients with ICH in the EPILOG study is suggestive of an additive effect of heparin, aspirin and Abciximab on intracerebral bleeding, particularly when standard dose heparin is used and the target ACT is high.

Table 37 Stroke Or ICH Within 6 Months Confirmed By Neuro CEC

Patients with events	Placebo	Reo Lo Hep	Reo Std Dose
Any Stroke or ICH n %	1 0.1 %	5 0.5 %	7 * 0.7 %
Hemorrhagic Stroke n %	0	1 0.1 %	2 * 0.2 %
Other # n %	0	1 0.1 %	2 0.2 %
Non hem Stroke n %	1 0.1 %	3 0.3 %	4 * 0.4 %

* 1 pt had both a nonhemorrhagic and hemorrhagic stroke
# subdural hematoma in 2 patients

The following table presents the incidents of hemorrhagic and nonhemorrhagic stroke by timing and survival status for each treatment arm. There were 4 patients who were found by the Neuro CEC to have had events but were without adequate documentation to classify the events in the Low Dose arm, and 2 each in the placebo and Std Dose arms. Those patients are included in the table.

Table 38 Timing Of Neuro Events Within 6 Months Reviewed By CEC (excludes events classified by CEC as TIA and as no event)

Events Reviewed	Placebo (n =3)	ReoPro Lo Hep (n = 10)	ReoPro Std Hep (n = 9)	Outcome at 6 mo
Within Index Hospitalization				
Nonhem Stroke	–	–	–	
ICH	–	1 (2 hr)@	2 (8!, 10 hr)	All Death
Unclassified	–	–	–	–
To 30 days				
Nonhem Stroke	–	1 (8 day)*	1 (28 day)	Alive, Alive
ICH	–	–	2 (18, 28 day) •	Both Alive
Unclassified	–	–	–	–
To 6 months				
Nonhem Stroke	1 (158 day)	2 (33, 85 d)	3(36, 76, 186 d)	All Alive
ICH / ICB	–	1 (72-78d)^	–	Alive
Unclassified	2 (2 mo, 5-6 mo)	5 (40, unknown, 127+, 181 d, 5 mo)	1 (83 d)	Death, Alive All Alive

! Subdural and Subarachnoid
@ Assoc w/ MI; cause of death uncertain
*Basal ganglia Lacune
• Pt at 28 days had both hemorrhagic and nonhemorrhagic stroke Pt at 18 days had a Cerebellar bleed
^Subdural Hematoma
+ Patient died at day 280 of a second stroke

The incidence of intracerebral bleeding was low in all treatment arms, however, there were no cases occurring during the index hospitalization in the placebo arm in this trial. There were 2 cases of ICH during the index hospitalization in the ReoPro Standard Dose Heparin arm. In both cases, the ACT during the procedure was quite high (394 and 405 were the maximal values observed), and it is likely the heparinization contributed to the bleeding. An interaction with the antiplatelet effects of Abciximab is also possible, as both bleeds occurred during the 12 hour Abciximab infusion time.

There was one case of ICH occurring during the index hospitalization in the ReoPro-Lo Dose Heparin arm, a right frontal subdural hematoma, which was surgically evacuated, but unsuccessful, and the patient expired. (It is not clear whether the ICH was the cause of death as the patient also sustained an MI.) The patient's maximal ACT was 250 during the procedure, and the platelet count was normal. It is likely the bleed in this case was due to a combination of the anticoagulation and antiplatelet effects of heparin, aspirin and Abciximab.

Reviewer Comment: These data are suggestive of additive effects of Abciximab, heparin, and aspirin in causing intracerebral bleeding. Taken together with the other bleeding data from this trial, these data strongly suggest that the combination of Abciximab and standard dose heparin should be avoided because of the increased bleeding risk..

7. Effect on Platelet Counts

Overall, 2.2 % of patients in the trial had thrombocytopenia. The median percent decrease was only slightly greater in ReoPro arms from study agent start until discharge 14%, 15 % vs 11 % placebo, and within 12 hours of start of study agent (11%, 12 % vs 8 % in placebo). Between 12 hours and the time of hospital discharge, the decrease was less in the ReoPro Low Dose Heparin arm than in the placebo arm (6.9 % vs 8.8 %). Table 39 shows a greater number of patients in the Abciximab arms had platelets decreased under 100,000, but the Abciximab standard dose heparin arm had the largest number of patients with platelets less than 50,000. Note: 3 patients with platelets < 50,000 DIED (2 in the ReoPro Standard Heparin arm, 1 in the placebo arm).

Table 39 Patients with Thrombocytopenia

	Placebo (n = 939)	ReoPro Lo Dose (n = 935)	ReoPro Std Dose (n = 918)
PLT < 100,000	14	23	24
PLT < 50,000	4	4	8

Reviewer Comment: These data suggest that while both heparin and Abciximab may contribute to thrombocytopenia, the combination of Abciximab with Standard Dose Heparin may be the most likely to cause severe thrombocytopenia and should be avoided.

8. Other Adverse Events

Only 1 major retroperitoneal bleed was seen in the trial; it occurred in the Placebo arm. There were 2 retroperitoneal bleeds that were classified as minor, in the ReoPro Standard Dose Heparin arm. There was no significant difference among treatment arms in other adverse events overall or in any organ system.

9. Relatedness to Study Drug

A total of 59 patients had serious adverse events that were considered reasonably related to study drug. The highest proportion occurred in the ReoPro Standard Dose Heparin arm (3.3 % vs. 1.5 % in the placebo arm, p = .0014. The proportion in the ReoPro Low Dose Heparin arm was not significantly higher than that in the placebo arm (2.2 %).

10. Treatment Discontinuations Due to Adverse Events

Overall 2 % of patients had the dose of study drug decreased or discontinued due to adverse events. Most cases were for bleeding. The incidence was lowest in the ReoPro Low Dose Heparin arm (1.4 %), and higher in the placebo arm (1.8 %), and highest in the ReoPro Standard Dose Heparin arm (2.9 %).

11. HACA Results

Serum samples were obtained only on patients in the Angiographic Substudy and assessed for HACA response at baseline, 30 days, and 6 months. Of the total 286 patients in this substudy, there were 131 who were evaluable (had serum samples at all 3 timepoints and were treated with Abciximab). The total incidence of positive HACA responses in all Abciximab-treated patients who were evaluated was 6.1 % , or 8 of 131 patients. This included 5 (7.7%) in the Abciximab plus low dose heparin arm, and 1 (1.6 %) s in the Abciximab plus standard dose heparin arm, and 2 of 3 placebo patients who had received open label ReoPro during the index hospitalization. Titers were low; 1:50 in 3 patients, 1:100 in 3 patients, 1:400 in 1 patient and 1:1600 in 1 patient.

Reviewer's Note: Results in the EPIC trial indicated 6.5 % of patients developed HACA antibodies with similar followup. Values were drawn at 4 and 12 weeks post treatment.

12. Readministration of Abciximab

Abciximab was known to have been readminstered to 15 patients during the EPILOG study, 5 in the Abciximab-low dose Heparin arm and 10 in the Abciximab-Standard dose Heparin arm. The interval ranged from approximately 1 month to 6 months. There were 2 patients who had previously been treated with Abciximab in the EPIC trial who were randomized to the Abciximab plus standard dose heparin arm of the EPILOG trial and were HACA negative during EPIC trial followup.

An allergic reaction was observed in one patient shortly after the initial administration of Abciximab. The reaction resolved with treatment with Benadryl and steroids. Study drug was discontinued after the patient had received one hour of the planned 12 hour infusion. This patient was readministered Abciximab at 187 days post randomization, and no adverse events were noted.

One patient had face and chest redness with pruritus following readministration of Abciximab at 75 days post randomization for a repeat percutaneous intervention. The reaction required no treatment. This same patient had thrombocytopenia (nadir 73,000, resolved spontaneously) after initial administration of Abciximab during the initial hospitalization.

Reviewer's Note: Readministration of Abciximab without incident in the first patient discussed above suggests that the allergic reaction observed after the first treatment may have been due to another etiology. There is a possibility in the second case discussed above that an immune response secondary to readministration of Abciximab may have been responsible for the facial redness and pruritus seen. HACA data are not available on these patients.

13. Vital Signs and Laboratory Effects

No significant differences in among treatment arms were seen on any of the vital signs or laboratory parameters measured.

B. Exploratory Analyses

1. Effect of Sheath Removal and Heparin Duration on Bleeding

The protocol recommended removal of the arterial sheath within 6 hours after removal of completion of the index procedure (guidewire removal). Investigators frequently took the option of continuing the sheath in position for longer, (n = 1437 $\leq$ 6 hrs, n = 1140 $>$ 6 hrs).

No significant difference are seen in the sponsor's analysis of bleeding events with sheath removal at $\leq$ 6 hours of guidewire removal or $>$ 6 hours.

ACTs at sheath removal were largely below 175. However, sheath site bleeding was more common among patients with ACT greater than 175 seconds or aPTT greater than 50 seconds (see Table 40). Among patients whose ACT was above this level at the time of sheath removal, the rate of major sheath site bleeding complications was greater among patients in both Abciximab arms. The highest rates of sheath site bleeding were also seen in patients in the Abciximab standard dose heparin arm, irrespective of the ACT value.

Among patients whose ACT or aPTT met the protocol specified values prior to sheath removal, the incidence of sheath site bleeding was highest among patients in the abciximab plus standard dose heparin group (7.3 %) , lowest among patients in the (3.6 %) placebo group, and intermediate among patients in the Abciximab low dose heparin group. This suggests that regardless of the heparin regimen, the level of anticoagulation at the time of sheath removal is a major predictor of bleeding.

Table 40 Patients With Sheath Site Bleeding By Level Of Anticoagulation At Time Of Sheath Removal

Treated Patients	Total (n = 2173)	Placebo (n = 923)	ReoPro Lo Dose (n = 923)	ReoPro Std Dose (n = 906)
ACT ≤ 175 or PTT ≤ 50 Patients w/ prolonged bleeding, hematoma > 5 cm, or RP Bleed	2173 117 5.4 %	717 26 3.6 %	743 39 5.2 %	713 52 7.3 %
ACT > 175 or PTT > 50 Patients w/ prolonged bleeding, hematoma > 5 cm, or RP Bleed	74 11 14.9 %	28 1 3.6 %	15 3 20.0 %	31 7 22.6 %
Patients not evaluated	505 44 8.7 %	178 10 5.6 %	165 13 7.9 %	162 21 13.0 %

There were more patients in the placebo and Abciximab-standard dose heparin arms who received heparin for more than 24 hours after the end of the index procedure. A greater percentage of the patients so treated had major bleeds than did patients treated with a shorter infusion (Table 41).

Table 41 Major Bleeding by Heparin Duration After Index Procedure

	Placebo (n = 939)	ReoPro Lo Dose (n = 935)	ReoPro Std Dose (n = 918)
Patients with intervention attempted	923	923	906
Patients receiving heparin after procedure	294	249	225
< 12 hour infusion Patients w/ major bleeds %	90 2 2.2 %	86 2 2.3 %	77 6 7.8 %
12 - 24 hour infusion Patients w/ major bleeds %	160 1 0.6 %	138 3 2.2 %	127 0 0 %
> 24 hour infusion Patients w/ major bleeds %	12 1 8.3 %	1 0 0 %	20 0 0 %
Unknown duration Patients w/ major bleeds %	32 2 6.3 %	24 1 4.2 %	19 0 0 %

2. Major Bleeds in Patients With Bleeding History
No difference was observed in rates of major non-CABG bleeds in patients with and without a prior history of significant bleeding in this trial.

Reviewer Note: the rate of bleeding in patients in the EPIC trial who had a prior history of bleeding was significantly increased over that of patients without a prior bleeding history.

The ReoPro + Standard Dose Heparin arm showed the greatest number of bleeds in both patients with and without a history of bleeding, though there was no significant difference among treatment arms.

3. Bleeding By Heparin Administration
The protocol recommended, but did not require, that heparin be stopped at the end of the index intervention. This was done for 1,458 of the 2,572 patients who had an index intervention. Rates of major bleeding were low in these patients, 0.2 % in the placebo arm, and 0.6 % in the Abciximab Low Dose Heparin arm, and 1.6 % in the Abciximab Standard Dose Heparin arm.

Of the other patients in the study, the highest major bleeding rates were observed in those that had heparin continued after the procedure and restarted after femoral sheath removal. The number of patients in this group was smaller in all treatment arms, but the rates were substantially higher (2.4 to 6.3 %). This suggests a correlation between extent of heparin treatment and major bleeding in all treatment arms (Table 42).

Table 42 Major Bleeding by Heparin Duration

Patients with Major Bleeding	Placebo (n = 939)	ReoPro Lo Dose (n = 935)	ReoPro Std Dose (n = 918)
Patients w/ Heparin Stopped at End of Procedure	462 1 0.2 %	498 3 0.6 %	498 8 1.6 %
Patients w/ Heparin Stopped at End of procedure, Restarted after Sheath Removal	166 3 1.8 %	172 1 0.6 %	182 3 1.6 %
Patients w/ Heparin Continued until Sheath Removal	191 2 1.0 %	169 1 0.6 %	142 4 2.8 %
Patients w/ Heparin Continued after procedure and after sheath removal	103 11 4.2 %	80 5 6.3 %	82 2 2.4 %

4. Investigator Reported Bleeding
Investigator-reported bleeding was recorded for the time between randomization and discharge (or 7 days post randomization). Over half the patients in each treatment arm had Investigator reported bleeding; more in the ReoPro arms than in the placebo (heparin only) arm.

A small number had serious consequences; there were, however, no statistically significant differences between the ReoPro arms and the placebo arm (Table 43). There were 2 deaths reported due to bleeding in the ReoPro plus Lo Dose and ReoPro Standard dose arms (both due to ICH in the ReoPro Standard Dose Heparin arm, 1 due to ICH in the ReoPro Lo Dose Heparin arm, and 1 due to bleeding complications of cardiac surgery in the ReoPro Low Dose Heparin arm), and none in the placebo arm. There were an equal number of patients with serious hypotension in the placebo and the Reo Pro Standard dose heparin arms (5 each) but only 2 in the ReoPro low dose heparin arm. There were 12 patients with other serious adverse events related to bleeding in the ReoPro Standard dose arm, while the ReoPro low dose heparin arm had none.

Table 43 Investigator Reported Bleeding

	Placebo n=939	ReoPro Low Dose n=935	ReoPro Std Dose n=918
Patients with Investigator Reported Bleeding	420 (44.7)	529 (56.6)	574 (62.5)
Deaths due to bleeding	0	2	2
Other serious AE due to bleeding	5	0	12
Serious Hypotension due to bleed	5	2	5

Reviewer Note: The higher rates of bleeding in the ReoPro Standard Dose Heparin arm strongly suggests the use of the combination of Abciximab and Standard dose heparin is not desirable.

VII. Interim Analysis Results

A decision was made by the SEMC to stop the trial after the Interim Analysis of results on the first 1500 patients due to strikingly positive efficacy findings in the ReoPro treated patients compared to placebo, with the best findings in the low dose heparin arm (see table 44). The primary endpoint of this analysis was death and MI at 30 days.

Table 44a Interim Analysis -- Death And MI At 30 Days

Patients w events	Total n = 1500	Placebo n = 492	Reo Lo Hep n = 510	Reo Std Dose n = 498
Finalized Analysis n % p value*	 75 5.1 %	 42 8.6 %	 15 3.0 % .00006	 18 3.7 % < .00001

* Logrank Test, Sig < .05

Reviewer Note: SEMC communications have been reviewed. It appears the integrity of the data was not compromised in the process, and that procedures were followed as outlined in the protocol and analytic plan for the study.

Note that according to the Analytic Plan, if the trial was stopped early for efficacy, the composite of death and MI at 30 days became the primary endpoint for the trial, superseding the prespecified primary composites which included urgent revascularizations at 30 days and repreat revascularizations at 6 months. Table 44b presents the endpoint of death and MI at 30 days for all 2,792 patients.

Table 44b Final Analysis -- Death And MI At 30 Days

Patients w events	Placebo n = 939	Reo Lo Hep n = 935	Reo Std Dose n = 91
n %	85 9.1 %	35 3.8 %	38 4.2%
p value*		< .0001	< .0001

* 1 sided Logrank Test, Sig < .05

VIII. Primary STENT Substudy

Initially, patients who were to be receiving STENT placement as primary treatment for coronary artery stenosis were excluded from participation in the EPILOG study. Due to the growing use of primary intracoronary STENTing, a substudy was incorporated into the larger trial to evaluate the concurrent use of Abciximab and STENTS with a protocol amendment in June 1995. A total of 123 patients were enrolled into the primary STENT substudy at 22 centers between August and December 1995.

Patients who were deemed suitable candidates for either STENT implantation or primary angioplasty for treatment of the target vessel were randomized into this substudy. Patients were randomized either to treatment with PTCA or primary STENT placement, and then to treatment with one of the 3 main treatment arms of the overall EPILOG study.

Of the 123 patient in the substudy, 65 were randomized to PTCA and 58 to primary treatment with a STENT. The distribution of patients was even across the 3 treatment arms of the main trial (see Table 45). Only 1 patient in the substudy was not treated with study agent; that patient was in the Abciximab Low Dose Heparin arm and randomized to PTCA. Unblinding of study agent or heparin occurred in only 2 patients in the substudy, one each in the PTCA and STENT arms. The PTCA and STENT groups were well matched on all demographic characteristics (see table 46).

Table 45 Distribution of Patients in Primary STENT Substudy

	Placebo + Std Hep	Abciximab + Lo Hep	Abciximab + Std Hep
PTCA	20	24	21
STENT	20	20	18

Table 46 Demographics of Patients in STENT Substudy

	PTCA (n = 65)	STENT (n = 58)
Male	50 (77 %)	44 (76 %)
Median Age (yrs)	61.5	61.1
Median Weight (kg)	65	58
Caucasian	57 (88 %)	52 (90 %)

Indications and Risk Status: The most common indication for the index intervention in substudy patients was unstable angina (42 %). Patients with recent MI comprised 25 % and patients with positive functional tests 23 %. These were similar to the proportions in the main study. Sixty-three percent of patients randomized to PTCA in the substudy were designated as high risk at randomization, as were 75 % of the patients randomized to STENT placement.

Concomitant Treatment: Heparin administration and ACT values during the procedure were generally similar to those of the overall study population. Post procedure heparin use was less common in substudy patients (15 % vs 28 % in the main study) in each of the 3 treatment groups. Ticlopidine was also administered to over 70 % of the patients randomized to STENT, and to 21 % of the patients randomized to PTCA in the substudy.

Treatment Received: STENTs were allowed for "bailout" of patients treated with PTCA. Of the 65 patients randomized to PTCA, 50 (77 %) had PTCA only, 14 (21 %) received at least one STENT, and 1 had failure to cross the lesion. Of the 58 patients randomized to STENT, 1 had PTCA only and 1 did not have treatment attempted.

Procedure Characteristics: The median duration of the index procedure was longer for STENT patients (40.5 minutes compared to 24.5 minutes for PTCA patients). The procedure was successful by angiographic outcome criteria for all lesions attempted in 93 to 95% of PTCA patients, and 97 to 100 % among patients randomized to STENT.

Primary Endpoint Events: The same primary endpoints were evaluated as in the main study. The Abciximab patients are combined for this analysis. Event rates at 30 days were lower with Abciximab than placebo for both PTCA and STENT patients (see Table 47), and at 6 months for PTCA patients but not for STENT patients. STENT patients fared better than PTCA patients in the placebo arm at both 30 days and 6 months, and STENT patients treated with Abciximab did slightly better than similarly treated PTCA patients at 30 days, but not at 6 months.

Table 47 Primary Endpoint Event Rates in PTCA or STENT Patients

	Placebo + Std Hep PTCA n = 20	Abciximab + Hep PTCA n = 45	Placebo + Std Hep STENT n = 20	Abciximab + Hep STENT n = 38
Death, MI or urgent revasc at 30 days	5 (25.0)	4 (8.9)	3 (15.0)	3 (7.9)
Death, MI, or repeat revasc at 6 months	10 (50.0)	11 (24.0)	4 (20.0)	11 (28.9)

Secondary Endpoint Events: Event rates were assessed for combined placebo and Abciximab groups. Fewer patients randomized to STENT had repeat revascularization at 30 days (composite 18.5 % PTCA patients and 10.3 % STENT patients). The composite including target vessel revascularization at 6 months was less common among patients randomized to STENT (32 % PTCA and 22 % STENT patients). The percentage of patients with a composite including death, MI, repeat revascularization or clinically significant angina (a novel endpoint combination in this substudy) was somewhat better among STENT patients (36 % PTCA and 31 % STENT patients).

Safety Results: Major bleeding occurred in 4.6 % of patients randomized to PTCA and 5.2 % of patients randomized to STENT. All major bleeds among STENT patients were related to sheath site bleeding, whereas all major bleeding events in PTCA patients were related to CABG. Minor bleeding occurred more frequently in STENT patients (6.2 % vs 1.7 % of PTCA patients). Transfusions of PRBCs were given more often to PTCA patients (7.7 %) than to STENT patients (5.2 %).

Reviewer Comments on the STENT Substudy:

Efficacy--the 30 day composite endpoint results favor the use of Abciximab in both patients undergoing PTCA and primary STENT placement. The factors responsible for the relatively poorer 6 month outcomes in STENT patients are not clear. It is difficult to draw conclusions regarding the efficacy of Abciximab in the setting of primary STENT placement due to the small numbers of patients treated in the substudy.

Safety--The occurrence of major bleeds in the STENT patients at the sheath site and higher rate of minor bleeds in the STENT patients may be explained by the treatment of the STENT patients with other antithrombotic agents, namely Ticlopidine, in addition to the heparin, aspirin, and Abciximab. This is consistent with the findings of the main study and of other studies that the risk of bleeding is increased in patients receiving multiple antithrombotic, antiplatelet, and/or thrombolytic agents concomitantly.

This study does not adequately assess either the risks or benefits of Abciximab treatment in conjunction with STENT placement.

IX. REVIEWER COMMENTS AND CONCLUSIONS

A. STUDY MANAGEMENT

1. The composition and performance of the CECs in reviewing endpoint events, and SEMC at interim and final analyses appear reasonable. The decisions and the integrity of data assessment procedures appear reasonably conducted as well.

B. STUDY CONDUCT

1. Randomization -the integrity of the randomization procedure to allocate patients to arms of the study appears reasonable. At issue is the scheme for allocation of patients enrolled to risk categories. Identifying patients prospectively (at randomization) by the likelihood of ischemic events should be the more clinically relevant assessment. However, the risk status of such a significant portion of the patients was changed at the time of CRF completion, that it casts doubt on the validity of the randomization categorization. The categorization performed at the time of CRF completion was subject to bias in that the ratings were done after the procedure had been completed and the lesion more extensively visualized, and in some cases, after the post-procedure hospital course was known. A more detailed and formalized assessment procedure was used, and thus the categorization procedure at the time of CRF completion may have favored more rankings in the high risk category. The Agency has requested that the sponsor perform an independent assessment of a sample of the pre-procedure angiograms in an attempt to validate the risk status assessment performed at randomization. The sponsor contends that a re-review will be likely to yield results differing from either the randomization or the CRF assessment, and that the ACC/AHA lesion classification system is not reliable enough to be used prospectively to categorize lesions with clinical relevance. The results of the angiogram re-review are pending at the time of completion of this review.

2. Blinding appears to have been reliably maintained in all treatment arms. The relatively small number of instances of unblinding do not appear to have compromised the integrity of the study.

3. Completeness of follow-up is good. There are a small number of missing values that have not impacted the results of the study.

C. EFFICACY FINDINGS

1. Success has been demonstrated on the 30 day primary composite endpoint, and the benefit appears sustained at 6 months It does appear that the agent can prevent cardiac ischemic complications secondary to coronary artery thrombus. These data confirm the results of the EPIC trial for patients at high risk. The claim for the extension of benefit to patients not deemed at such high risk cannot be determined from the data presented (see # 4).

2. Most of the benefit appears to be in prevention of myocardial infarction, most of which are large non Q wave MIs. There is also a trend toward reduction of Q wave MI, though the numbers of these events are smaller. There are fewer deaths in the ReoPro treated arms, but the numbers are too small to draw conclusions.

3. The 6 month primary endpoint shows benefit in the ReoPro arms by the sponsor's analysis using the logrank test on time to event data, although the magnitude is less than the benefit seen on the 30 day endpoint. When the proportion of patients with endpoint events at 6 months is compared using the Fisher exact test, there is no clear advantage seen in the Abciximab treatment arms.

The number of total revascularization procedures is not reduced in ReoPro treated patients at 6 months, particularly among high risk patients. This suggests that Abciximab does not retard the underlying atherosclerotic disease process in either the treated vessel or other coronary vessels. Results of the Angiographic Substudy will be reviewed separately.

4 Claim of Efficacy for Low and High Risk Subgroups -- Many of the patients who were initially determined to be of low risk status subsequently were reclassified as higher risk at the time of CRF completion, undermining the validity of the initial risk status assessment.

It is not clear which, if either, risk assessment represents a clinically reliable classification of the patients who are candidates for percutaneous coronary intervention. Examination of the primary endpoint confirms the efficacy of Abciximab in patients at high risk of ischemic cardiac events regardless of which classification is used. The as-randomized scheme also demonstrates efficacy in the low risk subset. The per-CRF results fail to support efficacy in the low risk subset, however.

Comment:

[redacted]

5. Efficacy across procedures other than balloon angioplasty is not as clearly established. There were few patients in the study with other procedures. However, the trends for those patients appear to be in the same direction.

D. SAFETY FINDINGS

1. Substantial improvement in bleeding rates was seen in all arms over that seen in EPIC trial. Weight adjustment of heparin, and the reduced duration and reduced dosage of heparin were the most important factors in reducing bleeding. Adherence to stricter anticoagulation guidelines and more stringent access site management appears to have significantly contributed to lowering the bleeding in all treatment arms compared to that seen in EPIC. Early sheath removal itself did not contribute much to the reduced bleeding, but discontinuation of heparin in order to get the ACT down prior to sheath removal was key.

2. There was no association of increased bleeding with lower body weight or gender, as seen in the EPIC trial.

3. Most bleeds occurred at the femoral arterial sheath site. There were more non-sheath site bleeds among patients in the Standard Dose heparin arms than in the Low Dose heparin arm.

4. The near double rate of minor bleeding (still a significant blood loss) in the ReoPro Standard Dose heparin arm, as well as the 2 cases of ICH in that arm, provide evidence that the ReoPro Standard dose heparin regimen is not a desirable combination.

6. The number of ICH is small overall, but the data suggest some additional risk may be introduced when ReoPro is added to heparin, either in standard or low doses.

7. The use of low dose weight adjusted heparin in combination with ReoPro appears to have the strongest safety profile of the 3 regimens compared.

X. RECOMMENDATIONS

A. Indication and Claims

1. Extension of benefit to patients not deemed at high risk of abrupt closure of the treated coronary artery rests on the resolution of the risk status assessment issue. At this time the supplement is not approvable for this extended patient population. Additional information has been requested from the sponsor to determine the reliability of the risk classification scheme used at randomization.

2. The study strongly supports the recommendation of the combination of weight adjusted heparin and reduced dosage and duration of heparin as concomitant therapy, along with adherence to stricter anticoagulation guidelines and more stringent arterial access site management, as means to reduce bleeding complications.

B. Labelling Comments

1. The safety data from the Abciximab low dose heparin regimen should be incorporated into labelling as soon as possible.

2. While the efficacy data from the EPILOG trial appear to indicate a benefit among the patients enrolled into the trial, the risk status of these patients is still under review. Efficacy data will not be included in the label at this time, until the risk status assessment issue can be resolved and the study results interpreted.

3. The sponsor presents data on intracranial bleed in aggregate from all trials completed to date. These data have been verified as supported by all 3 trials, and presentation of the aggregate statistic is appropriate.

4. The proposed label submitted by the sponsor also includes changes related to other studies. Comments are as follows:

   a) Extrapolation of the data from EPILOG on reduced bleeding to the unstable angina indication appears warranted, and the sponsor's recommendation that the lower anticoagulation target be adhered to during the PTCA for unstable angina patients receiving the 18 to 24 hour regimen is appropriate.

   b) The readministration study data will be discussed separately in that review.

   c) The EPIC data on _____ and the clinical pharmacology claims regarding the vitronectin receptor will be reviewed separately in BLA # 97-0201.

Appendix 1

CHARACTERISTICS OF TYPE A, B, AND C LESIONS

Type A lesions (minimally complex)
- Discrete (length < 10 mm)
- Concentric
- Readily accessible
- Nonangulated segment (< 45°)
- Smooth contour
- Little or no calcification
- Less than totally occlusive
- Not ostial in location
- No major side branch involvement
- Absence of thrombus

Type B lesions (moderately complex)
- Tubular (length 10 to 20 mm)
- Eccentric
- Moderate tortuosity of proximal segment
- Moderately angulated segment (> 45°, < 90°)
- Irregular contour
- Moderate or heavy calcification
- Total occlusions < 3 mo old
- Ostial in location
- Bifurcation lesions requiring double guidewires
- Some thrombus present

Type C lesions (severely complex)
- Diffuse (length > 2 cm)
- Excessive tortuosity of proximal segment
- Extremely angulated segments > 90°
- Total occlusions > 3 mo old and/or bridging collaterals
- Inability to protect major side branches
- Degenerated vein grafts with friable lesions

(From: Ryan et al. Guidelines for Percutaneous Translumin al Coronary Angioplasty: A Report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Committee on Per cutaneous Transluminal Coronary Angioplasty). J Am Coll Cardiol 1993; 2033-54.

CRF Page

Appendix 2

CENTOCOR

Phase III c7E3 Fab
EPILOG Trial

CENTOCOR STUDY NO. C0116T16 - _ _ _ _

PATIENT ENROLLMENT NO. _ _ _ _ _ _

PATIENT INITIALS _ _ _ _ _ _
first mid last

1

SEGMENT INFORMATION

Complete a separate page for each lesion undergoing treatment.

Segment #: _____

Procedure (by codes) in order used:

_____ _____ _____ _____ _____ _____

1 = PTCA 2 = DCA 3 = TEC Atherectomy 4 = Laser 5 = Rotational Atherectomy
6 = Stent Implantation 7 = Other FDA approved device, specify: _____

Primary Target Lesion? ☐1 Yes ☐2 No

Was this lesion subject to previous percutaneous intervention?
☐1 Yes ☐2 No ☐3 Unknown

PRE-INTERVENTION

TIMI Grade: _____ % Stenosis: _____

Check one column (lesion type) for each characteristic listed below.

	Type A	Type B	Type C
Length	☐1 <10 mm	☐2 10-20 mm	☐3 > 20 mm
Eccentricity	☐1 Concentric	☐2 Eccentric	
Accessibility	☐1 Readily Accessible	☐2 Moderate tortuosity of proximal segment	☐3 Excessive tortuosity of proximal segment
Lesion Angulation	☐1 < 45°	☐2 > 45° and < 90°	☐3 > 90°
Lesion Contour	☐1 Smooth	☐2 Irregular	
Ostial	☐1 Not ostial	☐2 Ostial	
Calcification	☐1 Little or none	☐2 Moderate to heavy	
Thrombus	☐1 Absent	☐2 Present	
Occlusion	☐1 Less than total	☐2 Total< 3 months old	☐3 Total > 3 months old
Bifurcation	☐1 No major involvement	☐2 Bifurcation lesions requiring dbl guide wires	☐3 Inability to protect major side branches
Grafts	☐1 NA		☐3 Degenerated vein grafts with friable lesion

INTERVENTION OUTCOME

Final TIMI Grade: _____ Final % Stenosis: _____

If % Stenosis > 50%, check reason(s) for failure: ☐1 Failure to cross
☐2 Failure to dilate
☐3 Abrupt closure
☐4 Dissection
☐5 Other: _____

Stent(s): ☐1 Yes, specify time: _ _ : _ _ (24 hr clock)
☐2 No

If Yes: Type (See code list) Size

_____ _____ mm
_____ _____ mm
_____ _____ mm

Codes for Types of Stents
1 = Palmaz Schatz
2 = Gianturco-Roubin
3 = Wiktor
4 = Other, specify on line

Was the patient referred for urgent CABG for a complication in treating this segment? ☐1 Yes ☐2 No

Dissection: ☐1 None ☐2 Minor ☐3 Major
If present: ☐1 Transverse ☐2 Longitudinal ☐3 Spiral

Perforation (angiographic evidence of true vascular perforation):
☐1 None ☐2 Localized ☐3 Tamponade

Thrombus/Filling Defect (Check all that apply):
☐ None ☐ Haziness ☐ Discrete Defect ☐ Contrast Staining

Distal Embolization: ☐1 None ☐2 Present

Temporary Coronary Occlusion? ☐2 None ☐1 Present
If present: Minimum TIMI grade: _____

Side Branch Occlusion (check one):
☐1 None ☐2 Small ☐3 Medium ☐4 Large ☐5 Not Applicable

Other interventions (Check all that apply):
☐ Perfusion catheter ☐ Other: _____
☐ IABP ☐ None
☐ Thrombolytics

phc 10-MAR-1995

Investigator's Signature: _____ Date: _ _ - _ _ _ - 19 _ _ (D-M-Y)

1/2

Appendix 3

ENROLLMENT FORM

Site# C0116T16
Patients Initials
Study Number
Kit #

TO RANDOMIZE A PATIENT, CALL 1-800-545-DUKE (3853)
Do not call earlier than 2 hours prior to index intervention

Date of enrollment ____/____/____ (dd-mon-yr)
Date of birth ____/____/____ (dd-mon-yr)

Enrollment time ____:____ (24-hr clock)
Weight ____ kg
Is the patient a diabetic ? YES or NO
Gender: Male or Female

History of MI YES or NO
if yes...Has the most recent MI occurred within 7 days? YES or NO
if yes...Is index intervention on the IRA? YES or NO

Please obtain written informed consent and complete the following information PRIOR to calling for Randomization

This Patient:		TRUE	FALSE
1.)	is at least 21 years old and, if a woman of child-bearing potential, has been made explicitly aware that c7E3 Fab may cause excessive menstrual bleeding and increased risk of uterine bleeding which could affect implantation of an ovum or cause abortion	☐	☐
2.)	is referred for elective or urgent percutaneous coronary intervention with an FDA approved device	☐	☐
3.)	has a target artery (native or graft) stenosis of ≥ 60% (visual estimation)	☐	☐
4.)	has provided written informed consent before enrollment and has agreed to comply with all protocol-specified procedures	☐	☐
5.)	has NOT dad unstable angina / non Q wave myocardial infarction meeting EPIC criteria within the previous 24 hours	☐	☐
6.)	has NOT had acute Q-wave myocardial infarction meeting EPIC criteria with onset of chest pain within the previous 24 hours	☐	☐
7.)	does NOT have active internal bleeding, a history of hemorrhagic diathesis	☐	☐
8.)	has NOT had major surgery or serious trauma within 6 weeks before study enrollment	☐	☐
9.)	has NOT had GI or GU bleeding of clinical significance within 6 weeks before enrollment	☐	☐
10.)	has NOT had a CVA within 2 yrs. before enrollment, or any CVA with residual neurological deficit	☐	☐
11.)	does NOT have intracranial neoplasm, arteriovenous malformation or aneurysm	☐	☐
12.)	has NOT had puncture of noncompressible vessel within 24 hrs prior to enrollment	☐	☐
13.)	does NOT have confirmed HTN with SBP>180mmHg or DBP >100mmHg	☐	☐
14.)	is NOT receiving oral anticoagulants (eg. warfarin) at time of enrollment	☐	☐
15.)	does NOT have baseline PT measurement >1.2 times control in the absence of heparin therapy	☐	☐
16.)	either does NOT have a >50% stenosis in the left main artery or, if > 50% occluded, the left coronary system is protected with at least one patent bypass graft	☐	☐
17.)	is NOT scheduled for rotational atherectomy	☐	☐
18.)	is NOT scheduled for stent implantation in a patient not suitable for enrollment into the Primary Stent Substudy	☐	☐
19.)	has NOT had percutaneous coronary intervention within the previous 3 months	☐	☐
20.)	does NOT have a presumed or documented history of vasculitis	☐	☐
21.)	does NOT have a known allergy to 7E3 or other murine proteins	☐	☐
22.)	does NOT have known allergy or intolerance to aspirin	☐	☐
23.)	has NOT participated in other clinical research studies involving the evaluation of other investigational drugs or devices within 7 days of enrollment	☐	☐

Specify most severe coronary artery morphological characteristics at the time of randomization in any artery to be treated during the index intervention (ACC/AHA criteria):

____ One type B ____ ≥ Two type B ____ ≥One type C ____ None of the above

Do you plan to enroll this patient in the stent substudy ☐ ☐

COMPLETE FOR ANGIOGRAPHIC SUBSTUDY PATIENTS ONLY:
Specify Primary Target Lesion:____ (Use lesion segment code from back of this form)

2.0 RISK ASSESSMENT IN THE EPILOG TRIAL

This supplementary review discusses the sponsor's response to the Agency Information Request submitted July 21, 1997.

I. Background

A. Issue: The sponsor [redacted] At randomization, only 35% of patients appeared to be classed as low risk. Further, the as randomized assessment of patient risk status differs from the assessment made on the CRFs; over half the patients originally classified as low risk at randomization were reclassified to high risk based on the CRF, leaving only 19% of patients in the trial classified as low risk by CRF. By the CRF classification, efficacy on the primary endpoint is not demonstrated in the patients in the low risk group (the number of patients and number of events becomes very small). This calls into question the reliability of the randomization risk assessment in defining patients' risk status with accuracy. Further, the CRF classification appears to identify a small subset of patients for whom the risk of cardiac ischemic complications is not high, and who derive no benefit from treatment with Abciximab.

The randomization assessment was based on a review of the patients clinical history and a relatively cursory review of the screening angiogram to determine if the patient had any Type B or C characteristics which would render them high risk. The CRFs were completed based on more detailed criteria regarding lesion morphology after completion of the index procedure, and in some cases after the patient's hospital discharge. Thus the CRF assessment was not made in the same way as the randomization assessment.

B. Steps Taken To Resolve this Issue: Telecons were held with the sponsor and two Information Request letters were sent by the Agency. The Agency has requested that the sponsor perform a reanalysis of a random sample of the screening angiograms in order to establish that the randomization risk status assessment was made in an unbiased manner, and that a similar assignment of risk status would be made by an independent observer. The sponsor has agreed to perform such a study and is preparing a protocol. This submission is provided to fulfill the Agency request for safety data by the risk subgroups, and as part of the continuing dialogue regarding these issues.

II. Review of This Submission

A. Contents The sponsor has included in this submission:

1. An explanation that the randomization risk assessment involved assessment of patients risk status as to whether or not they met the criteria used in the EPIC trial.

2. Bleeding data categorized by as randomized and CRF Risk status

3. A risk / benefit analysis demonstrating no significant additional risk of administration of Abciximab to the very low risk patients.

4. Data from the Angiographic Substudy, comparing the Core lab reviewers' risk status assessment with the assessment made by the investigators on the CRFs. They show that the subset of angiograms reviewed (286) is representative of the entire study population. They contend that this satisfies the need for an independent blinded review of pre-procedure angioagrams.

5. References on interobserver variability, to support their position that interobserver agreement is unlikely in any rereview of angiograms.

B. Sponsor's Discussion of the Issues

1. Comparison to EPIC risk assessment -- the sponsor explains that patients were screened at randomization as to whether or not they fit the criteria used in the EPIC trial to define patients at high risk patients. This screening was conducted in the same manner as that in the EPIC trial. The AHA/ACC guidelines for lesion morphology were used as the basis for risk status assessments, as they were in the EPIC trial. The determination was made prospectively, in advance of treatment or procedure outcome.

The sponsor has invoked a number of factors which could be responsible for the different readings:

1. Interobserver and intraobserver variability: in many cases the interventionalist who performed the procedure and completed the CRF was a different individual from the referring cardiologist who read the initial screening angiogram. They contend that it is to be expected that rereview would lead to uncovering new findings (more complex lesion characteristics) than to "take away" previous findings.

2. A structured approach to collection of lesion morphology data was not provided at the time of randomization. A less detailed categorization system was used.

3. Bias in the risk assessment made on the CRFs due to knowledge of the procedural outcome and , in some cases, the patient's hospital course.

4. Better visibility of lesions on the post procedural angiograms. Screening angiograms were most often viewed on a video system, which blurred and obscured some of the detail of the lesions. During and after the procedure, a digital system was used which permitted better visibility of the individual characteristics of the lesions.

5. An imperfect classification system.

The sponsor explains that the randomization risk assessment was planned by the investigators to simulate the assessment that is made in actual clinical practice. It was planned so that it could be done expeditiously and would not impact on patient care. They contend that the randomization risk assessment is the clinically relevant of the two assessments made, and that the data should be viewed based on the categorization made at this time. Additionally, they contend that the very low risk subgroup of patients can only be identified retrospectively in an analysis similar to that made on the cRFs; those with a very low risk of complications cannot easily be identified in advance of treatment with the agent or performance of the procedure. They explained further that the CRF review of lesion characteristics was performed for research purposes only, and that a detailed pre procedure review would have been inconsistent with clinical practice. This allowed the grouping of patients into a category that would have been eligible for treatment under the EPIC criteria (high risk) and those who would not (low risk).

C. Data on Efficacy by Risk Status

Data are presented showing that by the randomized risk classification, efficacy was demonstrated on the primary endpoint for both low and high risk patients when the Abciximab Low Dose arm is compared to placebo. The same is not true of the lower risk patients as classified by CRF data. They state, however, that the percent reductions for the Low Dose arm are consistent with overall trial results (see tables 1 and 2).

D. Data on Bleeding by Risk Subgroups

Tables 3 and 4 show bleeding events classified by risk subgroup at randomization and by CRF, respectively. The following can be seen from the data:

1. By either classification system, there appear to be higher rates of bleeding complications among high risk than among low risk patients, particularly major bleeding and RBC transfusion. (Note that minor bleeds appear increased in low risk patients compared to high risk by randomized category, but not by CRF category, and that the numbers are small).

2. Among the low risk patients based on CRF data, there were no patients with major bleeding in the Abcisximab plus low dose heparin arm, whereas 3 placebo patients experienced this complication. The sponsor provides data to show there was more spontaneous bleeding in the placebo treated patients also (5 vs none).

3. Thrombocytopenia appears sporadic and not significantly increased among the arms. There is a slightly higher percentage of cases in the Abciximab arms compared to placebo by both analyses. The sponsor provides case summaries, and notes that in none of these cases did platelets drop below 50,000, and that all cases resolved spontaneously without platelet transfusion

E. Risk Benefit Analysis

The sponsor has ranked safety and efficacy events in decreasing order of severity of clinical consequences to the patient:

Death
Stroke or other ICH
Urgent CABG or Q wave MI
Other urgent intervention or MI with peak enzymes ≥ 5x normal
Severe thrombocytopenia (< 50,000) or transfusion of platelets
PRBC transfusion or major bleeding with a spontaneous (non-instrumented) bleeding site
Other MI (peak enzymes < 5x normal or nonQ waveMI post index hospitalization
Other major bleeding
Other revascularization
Other thrombocytopenia (≥ 50,000)
Minor bleeding

Table 5 presents the number and percentage of patients in each treatment arm (placebo and Abciximab Low Dose Heparin) for the patients classified as low risk by CRF only. The column at the right extrapolates from the data and indicates the predicted cumulative benefit of patients treated with the Abciximab arm per 1000 patients treated (i.e. the number of patients who would have had these events if they had not been treated with Abciximab). No deaths or strokes occurred in either arm in this group. Through the first six items on the list, from urgent CABG/Q wave MI through spontaneous major bleeding, there is an advantage to treatment that translates into 23 per 1000. patients treated. Through other revascularization (the ninth item on the list), there appears to be an

advantage of 20 per 1000 patients treated. When the last two items are added (non-severe thrombocytopenia and minor bleeding), the balance begins to shift. The sponsor notes that the non-severe thrombocytopenia and minor bleeding events in the low dose heparin arm did not have any important adverse clinical consequences, thus the benefits of treatment appear to have outweighed the risks of treatment with Abciximab.

F. Angiographic Substudy Data

An Angiographic Substudy was conducted of 286 patients in the EPILOG trial. Patients at certain sites were randomized to the substudy, the purpose of which was to evaluate angiographic outcomes in these patients at 6 months, to assess the degree of restenosis following the index procedure. No study report has yet been submitted. Portions of the data from this substudy are cited in this submission by the sponsor as a means of evaluating interobserver variability in assessment of lesion morphology.

A blinded set of independent observers reread the intraprocedural angiograms for patients in the substudy. The criteria used to rate lesion morphology were those applied at the time of the CRF reading. Some items were not possible to assess blinded (age of a lesion or if a vein graft was present); in these cases, CRF data were used in order to keep the reviewers blinded. This allowed a comparison of the investigators' readings and of the core lab reviewers' readings on the lesion morphology criteria. These criteria were used as the basis for assessment of risk status, and overall assignments of risk category made.

The sponsor notes a high degree of variability and that mismatches occur in both directions (for example, 31 patients were classed as low risk by the core lab and high risk by the investigators, and 36 patients were classed as high risk by the core lab and low risk by the investigators), as shown in Figures 1 and 2. Note, however, that while there is considerable disagreement on the individual characteristics, and indeed on specific patients' lesions, there is a rather consistent overall assessment by both the investigators and the core lab on the percentages of patients whose overall risk status was high or low and the proportion of patients with A, B1, B2, or C as the most severe characteristics present in the lesions assessed.

Length, eccentricity, and presence of thrombus were the attributes on which the largest differences were observed (see Figures 3, 4, and 5).

G. References

Literature references are provided which point up the likelihood of great interobserver variability when angiograms are assessed by repeated observers.

1. Assessment of gross parameters such as presence or absence of lesions and percent stenosis showed relatively strong degrees of correlation between independent observers[1] (87 and 76%) in one study of coronary angiogram data in which panels were used to assess 1,830 pairs of angiograms with lesions for the Cholesterol Lowering Atherosclerosis Study. However, there was perfect agreement in only 54 percent of cases. More detailed aspects of lesion morphology were not assessed in this study. The authors state that the degree of agreement in their study was somewhat higher than that reported in the previous literature.

2. A study at the VA from 1975 is cited, in which 22 physicians read 13 angiograms on two different occasions. There was relatively good agreement about lesions in the right coronary artery and presence of ventricular aneurysm, but striking disagreement on assessment of LAD and LCx

lesions. Disagreement correlated inversely with experience in reading the angiograms[2].

3. An article by Stephen Ellis[3] is enclosed which discusses the data on which the ACC/AHA classification of risk status for abrupt arterial closure after mechanical intervention is based . Multivariate analysis was used to identify these factors based on data from 441 procedures, sampling from a total of 4,772. The six factors found to be the most powerful predictors of abrupt closure included a) post PTCA percent stenosis, b) dissection during the procedure, c) prolonged post PTCA use of heparin, d) branch point location, e) fixed bend point location, and f) other stenoses in the vessel dilated. These factors are not possible to assess prior to the procedure, and can only be properly assessed during or after the procedure itself.

4. Repeated readings of angiograms were done by different, and by the same observers in the Bypass Angioplasty Revascularization Investigation trial (manuscript in press). Of 391 readings of 72 angiograms, there was total agreement between all readers only 28% of the time. Of 181 repeat readings by the same observer, there was disagreement in 27% of the reads. The parameters assessed include the number of lesions for which angioplasty should be attempted and the location of the lesions[4].

5. A small study of four coronary angiographers who independently assessed 20 angiograms for the presence and degree of coronary stenosis is presented. This study showed a striking degree of variability in quantifying percent stenosis (ranges of 0 to 50, 10 to 90, 40 to 100 for specific lesions) and assessing the significance of lesions, particularly in the left main artery[5]. The investigators agreed on only 9 of the 20 angiograms (45 %).

The sponsor concludes that interobserver variability in the assessment of lesions will be great, and the ability of a reread of angiograms to validate a previous assessment may be limited by this.

III. REVIEWER COMMENTS:

3.0 THE INDEPENDENT ANGIOGRAM RE-REVIEW STUDY

A. Overview

This review concerns a re-review of baseline angiograms from patients in the EPILOG study submitted in response to the Agency's Information Request letter dated June 16, 1997. The Agency requested an independent review of a sample of baseline angiograms to establish confidence in the investigators' risk status assessment of patients based on the pre-procedure (baseline) angiogram (see the EPILOG Medical Officer's review, by this reviewer, and the Supplementary Review for the details of what led to this concern).

B. Objectives of the Angiogram Re-Review

The objectives of the study, as stated by the sponsor, were:

a) to assess the reproducibility of angiographic risk classification among independent reviewers,

b) to assess the reproducibility of the angiographic risk classification reported in the EPILOG CRF by independent reviewers, and

c) to assess the reproducibility of the angiographic risk classification performed at the time of randomization in the EPILOG trial by independent reviewers.

C. Study Methods

Angiographic films from a randomly selected subset of EPILOG patients were sent from the individual study sites to the Cleveland Clinic Angiographic Core Lab, where they were prepared for reading. Eighteen independent cardiologists were identified from a nationwide survey. These reviewers convened for simultaneous but independent reading of the angiograms at the Cleveland Clinic over a 2 day period. Readings were recorded on data collection forms and sent to Centocor for entry into a database and data analysis.

1. Selection of Reviewers

Reviewers were identified by a market research organization, [redacted]. Interventional cardiologists were recruited through a nationwide survey. They were told they would be participating in a study at the Cleveland Clinic to evaluate the utility of the ACC/AHA lesion classification system for patients undergoing coronary intervention. Physicians who had participated in the EPILOG trial were excluded from participation. Centocor was not involved in the selection process and was blinded to the identity of the participants until after the review was completed and the database was locked.

2. Reviewer Demographics

Eighteen interventional cardiologists were involved in the re-review. Only one of those 18 indicated that he did not use the ACC/AHA guidelines in clinical practice. They came from a variety of practice locations around the country; both academic and nonacademic institutions were represented. None were from the same practice. There were 17 fellowship training programs represented (2 had trained at Massachusetts General Hospital, in different years). Their average number of years in practice was 10; the range was 3.5 to 20. See Table 1 (next page) for a listing of re-reviewers.

THIS PAGE
WAS
DETERMINED
TO BE NOT
RELEASABLE

3. Selection of Angiograms for Review

The angiograms were selected from among a group of 530 randomly selected patients from the total of 2,792 patients in the EPILOG trial. Patients from the EPILOG trial were stratified by risk status at time of randomization and at time of CRF completion. Patients who had had an MI within 7 days were excluded from the selection process, as these would be classified as high risk by that criterion regardless of lesion characteristics.

Patients who had been assigned low risk status at randomization accounted for two thirds of the angiograms in the study. The main group of concern for the re-review was those who had changed from low risk at randomization to high risk by CRF. One hundred forty angiograms were randomly selected from that group (139 actually selected). One hundred angiograms were selected from the group that were low risk at randomization and low risk by CRF. Of those that were designated high risk at randomization, 50 were selected from those that were also designated high risk by CRF, and 70 (actually 71) were selected from those that were changed to low risk by CRF. See Table 2 below. The proportion sampled from each subgroup was determined prospectively with concurrence of the CBER review staff.

Table 2 Angiogram Sampling for Re-Review

Risk Status at Randomization	Risk Status by CRF Data	Number of Patients Films Re-Reviewed n = 360
Low	Low	100
Low	High	139
High	Low	50
High	High	71

4. Preparation of Films

Angiograms were forwarded by the study sites to the Cleveland Clinic Angiography Core Lab. The angiograms reviewed were not the actual pre-procedure angiograms, on which the randomization assessment had been based. In many cases, videotape was used in the cath lab for the baseline determination, and videotapes were no longer available. The films to be reviewed in this study were taken from the angiograms done during the index procedure. The Core Laboratory staff reviewed the films and spliced the films so that only the pre-intervention portion of the angiogram was available for review. The portion of the film showing the balloon and/or STENT, the procedure and the post-procedure images was edited out. The films were then pre-reviewed by the Cleveland Clinic Foundation (CCF) staff to confirm the identity of the lesion (s) being scored.

5. Logistics of Review

The re-review was conducted at the Cleveland Clinic Foundation. Ten reviewers reviewed films on the first day; 8 reviewers on the second day. Each reviewer was given a box of 20 films and directed to an individual review station. When review of the 20 films was completed, a new box was obtained. Each reviewer reviewed 60 films. They were allowed "as much time as necessary" to complete the task.

Each reviewer had his/her own review station. Reviewers were advised not to talk to one another about any review. Monitors were present to ensure that no discussions occurred between reviewers.

Each reviewer was given a packet of CRFs that matched the films. They recorded their responses, and returned these to the monitor. Each film was read by three (3) reviewers. A total of 1,080 reviews took place on the 360 films.

Data Collection and Management
A copy of the data collection form appears in Attachment 1. The forms were preprinted with patient identification numbers (EPILOG ID number), age, gender, and diabetes history (these were taken from the CRFs by Centocor), and the location of the lesion to be reviewed. The forms list brief descriptions of each lesion attribute category and checkboxes for completion by reviewers. A CCF staff member reviewed each form for completeness and to ensure that only one classification was checked for each attribute. Data forms were then forwarded to Centocor for data entry and analysis.

6. Data Evaluation / Statistical Methods
No formal hypothesis testing was involved. The kappa statistic was used as a measure of correlation of the agreement between reviewers' readings. Kappas were calculated for the re-review itself, and for the re-review compared to the CRF review, and for the re-review compared to the randomization review. Agreement was judged to be good if the kappa was ≥ 0.7 for each of the comparisons. For the re-review statistics, an average kappa value was derived by simulations (approximately 1200) making a random selection of one re-review for each patient and computing the kappa for this set of readings and the corresponding CRF or randomization classifications. The number of simulations were planned to ensure 99% confidence that the kappa value was accurate to within 0.01. The number of reviewers classifying patients as high risk was compared between subgroups using Cochran-Mantel-Haenszel statistics. Again, the Agency reviewers were in concurrence with the planned statistical methods, including the absence of formal hypothesis testing andthe establishment of the 0.7 criterion denoting good agreement.

7. Definitions Used
Lesions were classified by the most severe lesion characteristic, and patients then classified as high or low risk by the ACC/AHA guidelines used in the main EPILOG study (see Attachment 2). High risk patients were defined as those with any of the following characteristics:

- Stenosis with ≥ 1 type C characteristic in the artery to be treated, or
- Stenosis with ≥ 2 type B characteristics in the artery to be treated, or
- Age ≥ 65 years and female gender with ≥ 1 type B characteristic, or
- Diabetes mellitus and stenosis with ≥ 1 type B characteristic.

D. Study Results

1. Study Population
Demographics of the patients in the entire study, those eligible for re-review, and those in the re-review are listed in Table 3 on the next page. (All patients in the study except those with MI occurring within 7 days prior to enrollment were eligible). The average wight, height, and age are comparable between the re-review group and the overall group. The percentage of women was lower in the re-review group (21 % vs 28 % in the overall study), due to the over-sampling of low risk patients, because in women over age 65 only one type B lesion was required to classify a patient as high risk, thus a higher percentage of women were classified as high risk in the study overall.

The number, location, TIMI Grade and percent stenosis of the lesions reviewed are listed in Table 4 on the second page following. The table compares the re-review sample to the overall study population and to those eligible for re-review. The re-review group was similar to the larger groups on all parameters. Most patients had one native vessel with lesions attempted. A small percentage had grafts attempted. The location of lesions attempted was divided almost evenly among LAD, RCA, and LCX. Most patients (74 %) had one segment attempted. The minimum pre-intervention TIMI grade was 3 for 76 to 82 % of patients, and the maximum stenosis was 90% for all groups.

Table 3 Patient demographics: comparison of total EPILOG population and patients eligible for re-review in the angiographic re-review study

	Total (n = 2792)	Pts Eligible for Re-review (n = 2203)	Pts with Re-review of Baseline Angiograms (n = 360)
Gender			
Male	2012 (72.1%)	1576 (71.5%)	284 (78.9%)
Female	780 (27.9%)	627 (28.5%)	76 (21.1%)
Age (years)			
n	2792	2203	360
Mean ± SD	59.7 +/- 11.0	60.3 +/- 10.9	58.5 +/- 10.5
Median	60.0	61.0	59.0
Range	(29.0, 89.0)	(32.0, 89.0)	(32.0, 82.0)
Weight (kg)			
n	2790	2201	360
Mean ± SD	85.1 +/- 16.7	85.0 +/- 16.6	84.9 +/- 15.3
Median	84.0	84.0	84.0
Range	(44.0, 164.0)	(44.0, 164.0)	(44.0, 130.9)
Height (cm)			
n	2748	2168	357
Mean ± SD	172.3 +/- 9.9	172.1 +/- 10.0	172.6 +/- 10.1
Median	172.7	172.7	173.0
Range	(126.0, 205.7)	(126.0, 205.7)	(137.0, 193.0)
Race (n, %)			
Caucasian	2513 (90.0%)	1981 (89.9%)	327 (90.8%)
Black	167 (6.0%)	131 (5.9%)	14 (3.9%)
Oriental	7 (0.3%)	6 (0.3%)	2 (0.6%)
Hispanic	63 (2.3%)	51 (2.3%)	9 (2.5%)
American Indian	10 (0.4%)	7 (0.3%)	3 (0.8%)
Other	31 (1.1%)	26 (1.2%)	5 (1.4%)
Unknown	1 (0.0%)	1 (0.0%)	0 (0.0%)

Table 4 **Number of patients by number, location, minimum TIMI grade and maximum stenosis of lesions attempted during index intervention: comparison of total EPILOG population, patients eligible for re-review and patients in the angiographic re-review study.**

	Total (n = 2792)	Pts Eligible for Re-review (n = 2203)	Pts with Re-review of Baseline Angiograms (n = 360)
Pts with intervention attempted	2752	2203	360
Number of native vessels with lesions attempted			
0	84 (3.1%)	77 (3.5%)	6 (1.7%)
1	2439 (88.6%)	1935 (87.8%)	329 (91.4%)
2	227 (8.2%)	189 (8.6%)	25 (6.9%)
≥3	2 (0.1%)	2 (0.1%)	0 (0.0%)
Vessels with lesions attempted[a]			
Left main	6 (0.2%)	6 (0.3%)	0 (0.0%)
LAD	1034 (37.6%)	857 (38.9%)	132 (36.7%)
LCX	832 (30.2%)	660 (30.0%)	115 (31.9%)
RCA	1027 (37.3%)	796 (36.1%)	132 (36.7%)
Pts with grafts attempted	100 (3.6%)	93 (4.2%)	9 (2.5%)
Number of segments attempted[b]			
1	2050 (74.5%)	1635 (74.2%)	268 (74.4%)
2	573 (20.8%)	463 (21.0%)	78 (21.7%)
≥3	129 (4.7%)	105 (4.8%)	14 (3.9%)
Minimum pre-intervention TIMI grade in any target lesion			
0	205 (7.4%)	138 (6.3%)	21 (5.8%)
1	132 (4.8%)	99 (4.5%)	15 (4.2%)
2	251 (9.1%)	192 (8.7%)	24 (6.7%)
3	2105 (76.5%)	1732 (78.6%)	296 (82.2%)
Unknown	59 (2.1%)	42 (1.9%)	4 (1.1%)
Maximum pre-intervention stenosis in any target lesion (%)			
n	2751	2203	360
Median	90.0	90.0	90.0
Interquartile range	(80.0, 95.0)	(80.0, 95.0)	(80.0, 95.0)
Range	(47.0, 100.0)	(47.0, 100.0)	(50.0, 100.0)

[a] Some patients had more than one vessel with lesions attempted.
[b] Includes grafts

E. Inter-Reviewer Agreement Findings

The kappa statistic for the re-review was 0.29. The kappa for the re-review compared to the CRF assessment was 0.22. The kappa for the re-review compared to the randomization assessment was 0.09. These values indicate poor agreement among reviewers within the re-review, and among the re-review and each of the assessments conducted in the overall study (see Table 5 below). Agreement among the reviewers in the re-review was modest, but similar to the agreement of the re-reviewers with the CRF assessments. There was substantially less agreement of the re-reviewers with the randomization assessment.

Table 5 Overall Agreement by Kappa Values

Agreement Between	Kappa Value
Re-Review Alone (Inter-Rater)	.29
Re-Review and CRF	.22
Re-Review and Randomization	.09

Table 6 shows the number of reviewers (0, 1, 2 or 3) who classified a given patient as high risk. The table shows there was agreement among all 3 reviewers in 227 out of the 360 cases (63.1 %). One reviewer disagreed with the other two in evaluation of the other 133, or 36.9 %.

Table 6 Number of Re-Reviewers Classifying Angiogram as High Risk

	0	1	2	3
Number of patients	23 (6.4)	41 (11.4)	92 (25.6)	204 (56.7)

Table 7 shows the percent of lesions classified as high or low risk by the re-reviewers in each subgroup of risk status as categorized by randomization and CRF status. Sixty percent of the re-reviews indicated a high-risk classification for the group thought to be low risk by both randomization and CRF. Over eighty percent of the re-reviews indicated a high risk status for the group classified as low risk at randomization and reclassified as high risk at CRF. Over ninety percent or re-reviews indicated a high risk status for those categorized as high risk both at randomization and CRF.

Table 7 Number of reviews indicating low or high risk by risk status at randomization and risk based on CRF data

	Number of Pts Reviewed	Total Number of Patient Reviews	% of Reviews Indicating High Risk	% of Review Indicating Low Risk
Pts randomized as low risk				
Low risk based on CRF	100	300	60.3%	39.7%
High risk based on CRF	139	417	83.2%	16.8%
Pts randomized as high risk				
Low risk based on CRF	50	150	76.0%	24.0%
High risk based on CRF	71	213	91.6%	8.5%

Tables 8 and 9 compare the overall agreement between the re-review and the CRF and the re-review and the randomization assessments regarding high or low risk status. Overall, 65 % (697 of 1080) re-reviews were in agreement with the CRF reading. The Re-review readings agreed with the as-randomized readings in only 46 % of cases (498 of 1080).

Eighty-six percent of those read as high risk by CRF were read as high risk by the re-reviewers. However, 65 % of those read as low risk by the CRF reviewers were also read as high risk by the re-reviewers (only 34 % agreement). A similar proportion of agreement regarding high risk status is seen in the comparison with the randomization assessment (85.1 %). There was a greater level of disagreement with the low risk assessments made at randomization (73.6 % of those assessed as low risk at randomization were assessed as high risk by the re-review).

Table 8 Risk classification based on CRF data and re-review[a]

		Re-review		
		High	Low	Total
CRF	High	542 (86.0%)	88 (14.0%)	630
	Low	295 (65.6%)	155 (34.4%)	450
	Total	837	243	1080

[a] Results are presented as number and % of patients by risk classification by CRF evaluation (i.e. "row %")

Table 9 Risk classification based on randomization data and re-review[a]

		Re-review		
		High	Low	Total
Randomization	High	309 (85.1%)	54 (14.9%)	363
	Low	528 (73.6%)	189 (26.4%)	717
	Total	837	243	1080

[a] Results are presented as number and % of patients by risk classification at time of randomization (i.e. "row %")

The most severe lesion characteristic, classed as A, B1, B2 or C, for the re-review and for the CRF determinations are compared in Table 10. The overall agreement between the Re-review and the CRF readings is only 41 %, (448 of 1080 reviews). The Re-review reading was more severe in 42 % (455 of 1080), and the CRF reading was more severe in only 12 % (177 of 1080). From this table, it can also be seen that the majority of reviews were read as B2 by both the re-reviewers (587) and the CRF (459). However, more of the re-reviewers found lesions with C characteristics (212) than did the CRF (129). More of the CRF reviews found A or B1 as the most severe characteristic than did the re-reviews. The percentage agreement between the re-reviewers and the CRF reviews was highest among those classified as B2 (61.9 %) and lowest among those classified as A (15.2 %). The table shows also that when the re-review assessment differed, the re-review more often indicated a higher risk category, while there were also a substantial number of re-reviews indicating lower risk categories than the CRF.

Table 10 Most severe lesion characteristic based on CRF data and re-review[a]

		Re-review				
		A	B1	B2	C	Total
CRF	A	30 (15.2%)	57 (28.8%)	94 (47.5%)	17 (8.6%)	198
	B1	25 (8.5%)	74 (25.2%)	152 (51.7%)	43 (14.6%)	294
	B2	24 (5.2%)	59 (12.8%)	284 (61.9%)	92 (20.0%)	459
	C	3 (2.3%)	9 (7.0%)	57 (44.2%)	60 (46.5%)	129
	Total	82	199	587	212	1080

[a] Results are presented as number of lesion characteristics and % of lesion characteristics by CRF evaluation (i.e. "row %")

Table 11 **Most severe lesion characteristic based on randomization data and re-review[a]**

		Re-review				
		A	B1	B2	C	Total
Randomization	A	34 (12.2%)	56 (20.1%)	130 (46.6%)	59 (21.2%)	279
	B1	34 (6.7%)	101 (19.9%)	293 (57.8%)	79 (15.6%)	507
	B2	11 (4.5%)	39 (15.8%)	138 (56.1%)	58 (23.6%)	246
	C	3 (6.2%)	3 (6.2%)	26 (54.2%)	16 (33.3%)	48
	Total	82	199	587	212	1080

[a] Results are presented as number of lesion characteristics and % of lesion characteristics by lesion assessment at the time of randomization (i.e. "row %")

Table 11 (previous page) shows the same comparison for the re-review and the randomization assessments. The overall agreement between the Re-review and the as-randomized readings is only 28 % (289 of 1080). The Re-review readings were more severe in 675, or 62 %. The Randomization readings were more severe in only 116, or 10%. Three-quarters of the randomization assessments indicated A or B1 as the most severe lesion characteristic, while a similar proportion of the re-review assessments indicated B2 or C.

The individual lesion characteristics were assessed at both the CRF review and the re-review. The re-review revealed significant disagreement on which patients had Type A, B1 and C lesions. Most ratings fell into the A category on each of the individual characteristics. Comparison shows substantial disagreements in both directions on several important characteristics; the re-review consistently assessed lesions as more severe than did the CRF assessment (Table 12).

Table 12 Agreement Between Re-Review and CRF on Selected Lesion Characteristics[1]

Characteristic	Percent Agreement	% Assessed by CRF as More Severe	% Assessed by Re-Review as More Severe
Length	60 %	16 %	23 %
Accessibility	73 %	11 %	16 %
Contour	59 %	13 %	27 %
Eccentricity	58 %	13 %	28 %

1 Excludes a small number who were assessed as unknown by CRF or re-review

There was substantial agreement on assessment of other lesion characteristics, including angulation, calcification, ostial location, presence of thrombus, and occlusion.

Reviewer's Note: Individual lesion characteristics were not assessed at randomization, thus no comparison between the re-review and randomization data on lesion characteristics was possible.

F. Sponsor's Conclusions

The sponsor concludes that the low agreement among re-reviewers and among the re-reviewers and the as randomized and CRF classifications, indicates that risk status determined by the ACC/AHA angiographic risk criteria cannot be reliably reproduced by a group of experienced, practicing cardiologists. They state these results suggest that there is no reproducible way to identify, using these criteria, a low risk subgroup of the all-comers PTCA population enrolled in the EPILOG trial that will not benefit from Abciximab treatment.

G. Reviewer's Comments

There is a striking level of disagreement seen among the re-reviewers in this study. Responsible factors are likely to include differences in how the individual reviewers apply the criteria, biases acquired through practice experience, and perhaps less tangible effects of the review situation (travel time, fatigue, etc.) on individual performance.

There was a shift in risk level assessment towards a higher proportion of high risk assessments in both the CRF review and the re-review compared to the randomization review. It is possible that the formalized process of review requiring ranking specific lesion characteristics results in a bias toward higher risk assessments.

It is possible that the process of re-review outside the acute patient care setting leads to a closer examination of the films, and an inherent bias toward assessments of even higher risk status. The re-reviewers were told the purpose of the re-review was to establish the utility of the ACC/AHA lesion morphology rating system for high risk characteristics. The re-reviewers could have assumed most of the lesions reviewed would have high-risk characteristics, and had a bias toward favoring high risk readings. It is possible, though also less likely, that the group of reviewers selected was unusually diverse.

The fact that the films to be reviewed were taken from the actual intra-procedural angiograms, and the image quality was expected to be enhanced over that of the video images viewed at randomization, could have contributed to the readings differing more significantly from those made at randomization. The CRF assessments may have been affected by the bias of post-procedural knowledge of outcomes in some cases, but this does not appear to have been a major factor contributing to the different assessments.

It is likely that most or all of the above factors were operative in producing the level of disagreements seen among reviewers and among reviews. Therefore the criteria for lesion assessment, as applied in the EPILOG study, do not appear sufficiently reliable to have enabled adequate assessment of risk status.

H. Conclusions Regarding BLA # 97-0200

One of the two main objectives of the EPILOG trial was to evaluate the performance of Abciximab in a broader population of patients than the high risk patients enrolled in the EPIC trial. The sponsor has presented data indicating the patients enrolled in the EPILOG study were not at as high a risk for abrupt vessel closure, or for acute ischemic syndromes and their consequences, as were the patients in the EPIC trial. The highest risk patients in the EPIC trial, those presenting with acute MI and acute unstable angina, were excluded from the EPILOG trial. Thus the EPILOG population was distinct from the EPIC population. Efficacy has been established for the EPILOG population as a whole, and for patients in the trial who were regarded as at high risk for ischemic events. Efficacy has not as clearly been established for patients regarded as at lower risk for events.

The CRF risk assessments differed substantially from those made at randomization in the EPILOG study. The risk status subsets identified during the study were not reproduced in the independent angiogram re-review; those assessments differed signigicantly from the CRF assessments. Thus, the lesion classification system employed to identify patients in the EPILOG trial by risk status does not appear sufficiently reliable to recommend its use in stratifying patients by risk in advance of treatment. Therefore, the efficacy seen in the risk subsets in the EPILOG study may not be confidently generalized to the larger population.

By the randomization classification, the sponsor claims benefit is shown on the low risk subgroup. When the placebo event rates for patients randomized as low and those randomized as high risk in the EPILOG trial are compared, the patients identified as low risk do show a lower placebo event rate. However, it is uncertain that the randomization method of risk assessment would provide a reproducible result; thus the efficacy data for the subgroups should not be relied upon.

Comment: The as-randomized assessment employed an overall assessment of whether A, B1, B2 or C characteristics were present. That method has not been reproduced and has not been formally assessed in the re-review. Perhaps the randomization risk assessment is more reliable than the CRF assessment, but there is not adequate evidence to show this. It would require an independent angiogram re-review employing the films and the methods used at randomization to validate those assessments.

By the CRF determination, a subgroup of patients is identified who were thought to be low risk and demonstrated low placebo event rates; these patients do not appear to demonstrate significant benefit from the administration of Abciximab. By the re-review determinations, even fewer patients were identified as low risk, and event rates do not correlate as clearly with the assessments. Thus the efficacy data based on these subset analyses may not be relied upon either.

There are no data contradicting the sponsor's statement that the EPILOG trial enrolled "all comers", that is, all patients referred for coronary angioplasty, regardless of anticipated risk status. The sponsor has also submitted literature indicating that there are factors arising during coronary interventions which may change a patient from a lower risk to a higher risk category (dissection, thrombus formation, etc.). While it may be possible to discern risk status with greater certainty post-procedure, (once the procedural outcome and the clinical course of the patient is known), it is not possible to make that distinction prospectively.

The bleeding risk profile of Abciximab from the EPILOG study appears considerably improved over that which was seen in the EPIC trial when the lower dose, weight-adjusted and shorter duration heparin regimen is used concomitantly. The patients at greatest risk for significant bleeding complications do not appear to be the patients with lower cardiac risk profiles as identified at randomization. Thus there do not appear to be risks associated with treatment that would outweigh the potential for benefit in a broad population of patients.

For these reasons, it would not be appropriate to specifically state in product literature, labelling or advertising that low risk patients have been demonstrated to benefit (or not to benefit) from Abciximab treatment. It would be preferable to state in the product literature and labelling that it is not reliably possible to discern a patient's risk for ischemic cardiac complications prior to the performance of the procedure. There are not appreciable risks outweighing the potential for benefit for most patients referred for coronary angioplasty, and the product

Attachment 1

ANGIOGRAPHY REVIEW

The Cleveland Clinic Foundation, Cleveland, Ohio

August 2nd and 4th, 1997

Patient Identification		Demographics	
Patient Number:	12345	Age and Sex:	52 yrs Female
Patient Initials:	DLD	Diabetes:	Unknown
Date of Intervention:	26-Feb-1995	Date of most recent MI:	Nov-94

Lesion Identification

Lesion Location: SVG to Unknown

Number of Lesions: 2 of 4

CASS Lesion Number: 29

Check one column (lesion type) for each characteristic listed below. Do not leave a characteristic blank. In case of error, put a slash through the incorrect mark and date and initial. Mark and circle the correct entry.

Characteristic	Type A	Type B	Type C
Length	O_1 < 10 mm	O_2 10 to 20 mm	O_3 > 20 mm
Eccentricity	O_1 Concentric	O_2 Eccentric	
Accessibility	O_1 Readily accessible	O_2 Moderate tortuosity o proximal segment	O_3 Excessive tortuosity of proximal segment
Lesion Angulation	O_1 < 45 degrees	O_2 > 45 and < 90 degrees	O_3 > 90 degrees
Lesion Contour	O_1 Smooth	O_2 Irregular	
Ostial Location	O_1 Not ostial	O_2 Ostial	
Calcification	O_1 Little or none	O_2 Moderate to heavy	
Thrombus	O_1 Absent	O_2 Present	
Occlusion	O_1 Less than total	O_2 Total < 3 months old	O_3 Total > 3 months old
Bifurcation	O_1 No major involvement	O_2 Bifurcation lesions requiring double guide wires	O_3 Inability to protect major side branches
Grafts	O_1 NA		O_3 Degenerated vein grafts with friable lesions

Reader #: _____

Reader's Signature: _____ Date: __ __-__ __ __-19__ __ (D-M-Y)

Attachment 2

CHARACTERISTICS OF TYPE A, B, AND C LESIONS

Type A lesions (minimally complex)
- Discrete (length < 10 mm)
- Concentric
- Readily accessible
- Nonangulated segment (< 45°)
- Smooth contour
- Little or no calcification
- Less than totally occlusive
- Not ostial in location
- No major side branch involvement
- Absence of thrombus

Type B lesions (moderately complex)
- Tubular (length 10 to 20 mm)
- Eccentric
- Moderate tortuosity of proximal segment
- Moderately angulated segment (> 45°, < 90°)
- Irregular contour
- Moderate or heavy calcification
- Total occlusions < 3 mo old
- Ostial in location
- Bifurcation lesions requiring double guidewires
- Some thrombus present

Type C lesions (severely complex)
- Diffuse (length > 2 cm)
- Excessive tortuosity of proximal segment
- Extremely angulated segments > 90°
- Total occlusions > 3 mo old and/or bridging collaterals
- Inability to protect major side branches
- Degenerated vein grafts with friable lesions

(From: Ryan et al. Guidelines for Percutaneous Transluminal Coronary Angioplasty: A Report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Committee on Percutaneous Transluminal Coronary Angioplasty). J Am Coll Cardiol 1993; 2033-54.

4.0 THE ANGIOGRAPHIC SUBSTUDY OF THE EPILOG TRIAL

I. Overview

The Angiographic Substudy was a substudy within the context of the EPILOG trial. The objective was to compare the effects of the three regimens used on angiographic restenosis at 6 months post randomization. The substudy was planned to enroll 900 patients, but due to the main trial's early termination, enrolled less than one-third of this number, or 286 patients, at 17 sites.

The study report was not submitted with the licensing application supplement filed in February. The study report, containing data on angiographic and clinical outcome, was submitted just prior to the 6 month regulatory action date on BLA # 97-0200, and thus constituted a major amendment to that file. Hence, the substudy is reviewed here as a supplement to the main Medical Officer's Review of the EPILOG trial.

II. Substudy Protocol

A. Objectives

The objective of the Angiographic Substudy was to compare the effects of the three regimens used in the EPILOG trial in patients undergoing percutaneous coronary intervention with respect to angiographic restenosis at 6 months post randomization. Quantitative angiographic parameters were determined by computer-assisted analysis of coronary angiograms.

The incidence of HACA antibody responses was assessed in substudy patients, and have been reported with the main study report.

B. Investigators and Sites

Sites were selected which demonstrated expertise in performing high quality angiograms and in returning a high proportion of patients for follow-up angiography. All patients at the sites selected were enrolled in the substudy. Some of the sites selected were also participating in the STENT substudy, to ensure adequate representation of STENT patients in this substudy.

C. Study Design

The substudy protocol was submitted as an amendment to the EPILOG protocol dated June 15, 1995, well after the trial was underway.

The patients in all arms of the substudy were to receive the same treatment, according to study arm, as the other patients in the EPILOG trial. At 6 months (at least 184 days, not ≥ 275 days), substudy patients were to return to the study site for repeat angiography.

Quantitative computer assisted analysis of angiograms was to be performed by the Cleveland Clinic Angiography Core Laboratory.

D. Procedures

Angiograms were performed at baseline, at the end of the index intervention, and at 6 months in substudy patients. Every effort was made to perform follow-up angiograms at the same cath lab as the baseline films. Standard procedural guidelines were provided to all participating sites by the Core Lab. In some cases, a different lab performed the follow-up angiogram. In those cases, detailed instructions were provided to the lab to ensure the same procedural guidelines were followed.

All angiograms were analyzed by the Angiography Core Lab at Cleveland Clinic. The Core Lab

reviewers were blinded to study agent allocation. Lesions were assessed qualitatively by Core Lab reviewers and quantitatively using a previously validated computer-assisted technique. Logs were kept of films received, segments treated, angles of projection, and catheter sites.

Patients were not required to have a follow-up 6 month angiogram if:

- the patient had never received study agent (Abciximab or placebo)
- the index procedure was not attempted or was not successful in any of the attempted lesions (≥ 50 % residual stenosis)
- the patient had a CABG or repeat PTCA of all target vessels between randomization and the 6 month anniversary date
- repeat angiogram was done showing complete occlusion of all target lesions by the 3 month anniversary
- the patient had repeat coronary angiography for clinical indications between the 3 and 6 month anniversary dates

E. Endpoint Variables

1. Quantitative Angiographic Variables

The following parameters were studied:

- Minimum luminal diameter (MLD) at 6 months
- Late loss (MLD immediately post index procedure minus MLD at follow-up 6 months)
- Loss index (ratio of late loss to early gain; early gain = MLD post procedure minus MLD prior to procedure)
- Percent diameter stenosis

2. Qualitative Angiographic Variables

- Baseline TIMI grade
- Percent stenosis
- Morphological characteristics
- Angiographic success (residual stenosis ≤ 50%)
- Complications of treatment (dissection, thrombus, abrupt occlusion, distal embolization, side branch occlusion)

3. Clinical Outcome

The 30 day and 6 month primary endpoints evaluated in the main study were computed for patients in the substudy.

F. Sample Size Predictions

The sample size required was calculated as 210 patients per arm to detect a 15% improvement in minimum luminal diameter in either Abciximab arm compared to placebo. Allowing for 2 % of patients not initially treated with study medication or coronary intervention, 8 % of patients without acute procedural success, and 20% of patients without follow-up or technically inadequate angiograms, the planned recruitment was to be 300 per arm.

G. Statistics

Survival methods were used; pairwise comparisons were made of each of the Abciximab groups vs the placebo arm, and of the combined Abciximab groups vs the placebo, using the logrank test. Event rates were computed using the Kaplan Meier method.

III. RESULTS

A. Study Sites

The majority of the patients enrolled were drawn from the Cleveland Clinic (83), The Christ Hospital in Cincinnati (64), and Duke University Medical Center (21). Ten of the 17 sites were Canadian, and accounted for 92 patients. The remainder came from four other US sites. Table 1 shows the distribution of patients among sites.

Table 1 Sites Enrolling Patients into Angiographic Substudy

Site No.	Site	Principal Investigator	Patients Enrolled
11	Cleveland Clinic Foundation, Cleveland, OH	A. Michael Lincoff, M.D.	83
14	The Christ Hospital, Cincinnati, OH	Dean J. Kereiakes, M.D.	64
24	Duke University Medical Center, Durham, NC	James E. Tcheng, M.D.	21
61	Ottawa Civic Hospital, Ottawa, Ontario	Jean-Francois Marquis, M.D.	21
72	University of Alberta Hospital, Edmonton, Alberta	Jeffrey Burton, M.D.	17
73	Mount Sinai Hospital, Toronto, Ontario	Alan G. Adelman, M.D.	13
75	Royal Columbian Hospital, New Westminster, BC	Robert I. G. Brown, M.D.	13
34	University of Florida Health Science Center, Jacksonville, FL	Theodore Bass, M.D.	10
08	Rochester General Hospital, Rochester, NY	Gerald Gacioch, M.D.	9
74	Health Sciences Centre, Winnipeg, MB	John Ducas, M.D.	7
02	St. Louis University Hospital, St. Louis, MO	Frank V. Aguirre, M.D.	6
64	Victoria General Hospital, Halifax, NS	Blair J. O'Neill, M.D.	5
76	St. Boniface General Hospital, Winnipeg, MB	Po K. Cheung, M.D.	5
59	Vancouver General Hospital, Vancouver, BC	Donald R. Ricci, M.D.	4
66	Calgary Foothills Hospital, Calgary, AB	Merril L. Knudtson, M.D.	4
21	Graduate Hospital, Philadelphia, PA	Ronald Gottlieb, M.D.	2
77	Victoria Hospital Corporation, London, Ontario	David Almond, M.D.	2

B. Study Population

The distribution of patients across arms was similar, as shown in Table 2. STENT substudy patients accounted for 20 % of the patients in this substudy. Slightly more STENT substudy patients were randomized to PTCA, equally distributed across treatment arms (there were only 24 patients receiving primary STENTS in the angiographic substudy).

Table 2 Accounting of Angiographic Substudy Patients

	Total	Placebo + Std-Dose Heparin	Abciximab + Low-Dose Heparin	Abciximab + Std-Dose Heparin	Combined Abciximab Groups
Pts in Angiographic Substudy	286	95	102	89	191
Pts enrolled in Primary Stent Substudy	57 (19.9%)	17 (17.9%)	22 (21.6%)	18 (20.2%)	40 (20.9%)
Randomized to stent	24 (8.4%)	7 (7.4%)	9 (8.8%)	8 (9.0%)	17 (8.9%)
Randomized to PTCA	33 (11.5%)	10 (10.5%)	13 (12.7%)	10 (11.2%)	23 (12.0%)

C. Patients Lost to Follow-up

A total of 284 patients (99 %) had baseline films reviewed. Baseline films were lost for 2 patients; one did not receive study agent, the other had a failed intervention in all lesions attempted. No followup films were received by the core lab for these 2 patients.

A total of 230 patients (80%) had followup films reviewed. Table 3 shows the percentage was consistent across treatment arms, and lists the reasons the other 56 patients did not have followup films reviewed (20 patients refused, 8 were not treated with study agent, 8 had failed PTCA in all lesions). Of the 230 patients with followup films, only 157 (55%) had films done > 183 days post randomization. Fifty-five patients (19%) were done between 3 and 6 months, and 18 patients (6 %) were done at less than 3 months.

Table 3 Angiographic Follow up

	Total	Placebo + Std-Dose Heparin	Abciximab + Low-Dose Heparin	Abciximab + Std-Dose Heparin	Combined Abciximab Groups
Pts in Angiographic Substudy	286	95	102	89	191
Pts with films reviewed by Core Lab	284 (99.3%)	95 (100.0%)	100 (98.0%)	89 (100.0%)	189 (99.0%)
Index procedure	284 (99.3%)	95 (100.0%)	100 (98.0%)	89 (100.0%)	189 (99.0%)
Index procedure and follow-up	230 (80.4%)	74 (77.9%)	84 (82.4%)	72 (80.9%)	156 (81.7%)
≤3 mos post randomization	18 (6.3%)	5 (5.3%)	11 (10.8%)	2 (2.2%)	13 (6.8%)
>3- 6 mos post randomization	55 (19.2%)	19 (20.0%)	18 (17.6%)	18 (20.2%)	36 (18.8%)
>6 mos post randomization[a]	157 (54.9%)	50 (52.6%)	55 (53.9%)	52 (58.4%)	107 (56.0%)
Follow-up only	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pts with no follow-up films	56 (19.6%)	21 (22.1%)	18 (17.6%)	17 (19.1%)	35 (18.3%)
Pt not treated with study agent	8 (2.8%)	3 (3.2%)	4 (3.9%)	1 (1.1%)	5 (2.6%)
PCI not attempted	3 (1.0%)	1 (1.1%)	2 (2.0%)	0 (0.0%)	2 (1.0%)
PCI failed in all lesions	8 (2.8%)	4 (4.2%)	4 (3.9%)	0 (0.0%)	4 (2.1%)
Not required per protocol	8 (2.8%)	4 (4.2%)	1 (1.0%)	3 (3.4%)	4 (2.1%)
Pt died	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	1 (0.5%)
Pt refused	20 (7.0%)	6 (6.3%)	4 (3.9%)	10 (11.2%)	14 (7.3%)
Unable to schedule/ administrative	6 (2.1%)	2 (2.1%)	3 (2.9%)	1 (1.1%)	4 (2.1%)
Pt lost to follow up	1 (0.3%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Angiography contraindicated	1 (0.3%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Films lost	2 (0.7%)	0 (0.0%)	1 (1.0%)	1 (1.1%)	2 (1.0%)

[a] >183 days post randomization.

D. Study Agent Administration

Nearly all of the substudy patients (278, or 97 %) were treated as randomized. Eighty-one percent received the full dose overall; more had the dose discontinued early in the placebo arm than in the Abciximab arms, consistent with what occurred in the overall study (see Table 4).

Table 4 Number of Angiographic Substudy Patients Receiving Study Agent

	Total	Placebo + Std-Dose Heparin	Abciximab + Low-Dose Heparin	Abciximab + Std-Dose Heparin	Combined Abciximab Groups
Pts in Angiographic Substudy	286	95	102	89	191
Pts treated with study agent	278 (97.2%)	92 (96.8%)	98 (96.1%)	88 (98.9%)	186 (97.4%)
Full dose administered					
Yes	234 (81.8%)	70 (73.7%)	86 (84.3%)	78 (87.6%)	164 (85.9%)
No	40 (14.0%)	21 (22.1%)	11 (10.8%)	8 (9.0%)	19 (9.9%)
Unknown	4 (1.4%)	1 (1.1%)	1 (1.0%)	2 (2.2%)	3 (1.6%)
Pts not treated with study agent	8 (2.8%)	3 (3.2%)	4 (3.9%)	1 (1.1%)	5 (2.6%)

E. Demographics

Demographic characteristics were generally similar to those of the overall EPILOG study population, as shown in Table 5.

Table 5 Demographics of Angiographic Substudy Patients

	Total	Placebo + Std-Dose Heparin	Abciximab + Low-Dose Heparin	Abciximab + Std-Dose Heparin	Combined Abciximab Groups
Pts in Angiographic Substudy	286	95	102	89	191
Gender					
Male	210 (73.4%)	69 (72.6%)	76 (74.5%)	65 (73.0%)	141 (73.8%)
Female	76 (26.6%)	26 (27.4%)	26 (25.5%)	24 (27.0%)	50 (26.2%)
Age (years)					
n	286	95	102	89	191
Mean ± SD	59.6 +/- 10.6	59.5 +/- 11.3	59.2 +/- 10.8	60.0 +/- 9.8	59.6 +/- 10.3
Median	60.0	60.0	59.0	61.0	60.0
Range	(32.0, 83.0)	(36.0, 81.0)	(32.0, 83.0)	(39.0, 80.0)	(32.0, 83.0)
Weight (kg)					
n	286	95	102	89	191
Mean ± SD	84.2 +/- 16.8	81.9 +/- 14.9	83.6 +/- 17.1	87.2 +/- 18.2	85.3 +/- 17.6
Median	82.6	80.0	83.4	84.3	84.0
Range	(50.0, 164.0)	(55.0, 132.0)	(50.0, 163.0)	(50.0, 164.0)	(50.0, 164.0)
Height (cm)					
n	284	95	101	88	189
Mean ± SD	171.8 +/- 10.0	171.4 +/- 11.8	171.6 +/- 8.8	172.5 +/- 9.4	172.0 +/- 9.1
Median	173.0	175.0	173.0	172.6	172.7
Range	(126.0, 196.0)	(126.0, 191.0)	(152.0, 196.0)	(152.0, 193.0)	(152.0, 196.0)
Race					
Caucasian	267 (93.4%)	91 (95.8%)	94 (92.2%)	82 (92.1%)	176 (92.1%)
Black	13 (4.5%)	3 (3.2%)	5 (4.9%)	5 (5.6%)	10 (5.2%)
Oriental	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hispanic	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
American Indian	3 (1.0%)	0 (0.0%)	2 (2.0%)	1 (1.1%)	3 (1.6%)
Other	3 (1.0%)	1 (1.1%)	1 (1.0%)	1 (1.1%)	2 (1.0%)

F. Risk Status

Approximately 60% of patients in the substudy were classified as high risk at randomization. Note that this percentage is slightly higher in the placebo arm than in the Abciximab arms. Note also that the Core Lab classified patients differently than the randomization classification. The same lesion morphology characteristics were used to identify high-risk patients as those used in the overall trial. The classification scheme used by the core lab for lesion morphology differed slightly from the ACC/AHA classification, in the criteria for classification of angulation. The core lab was not able to classify certain attributes (bifurcation, degenerated vein grafts, age of a total occlusion); CRF data were used for these attributes. Clinical history was taken from the CRFs for risk status assessment.

Overall, 62 % of substudy patients were randomized as high risk and 37 % as low risk. This was consistent with the overall study (64 and 36% high and low risk, respectively). The Core Lab identified 79 % as high risk and 21 % as low risk, again similar to the reclassification seen in the overall trial when the more structured approach to lesion classification was used to complete the CRFs. (see Table 6)

Table 6 Number of Angiographic Substudy Patients by Risk Classification at Time of Randomization vs Risk Classification Based on Angiographic Core Lab Data

	Total	Placebo + Std-Dose Heparin	Abciximab + Low-Dose Heparin	Abciximab + Std-Dose Heparin	Combined Abciximab Groups
Pts in Angiographic Substudy	286	95	102	89	191
Pts randomized as high risk	179 (62.6%)	64 (67.4%)	61 (59.8%)	54 (60.7%)	115 (60.2%)
High risk based on Core Lab data	149 (52.1%)	57 (60.0%)	47 (46.1%)	45 (50.6%)	92 (48.2%)
Lower risk based on Core Lab data	28 (9.8%)	7 (7.4%)	12 (11.8%)	9 (10.1%)	21 (11.0%)
Unknown	2 (0.7%)	0 (0.0%)	2 (2.0%)	0 (0.0%)	2 (1.0%)
Pts randomized as lower risk	107 (37.4%)	31 (32.6%)	41 (40.2%)	35 (39.3%)	76 (39.8%)
High risk based on Core Lab data	78 (27.3%)	21 (22.1%)	28 (27.5%)	29 (32.6%)	57 (29.8%)
Lower risk based on Core Lab data	29 (10.1%)	10 (10.5%)	13 (12.7%)	6 (6.7%)	19 (9.9%)

G. Indication for the Procedure

The majority of patients were being treated for unstable angina (42%, similar to the overall study), followed by a positive functional test (25 %, more than there were in the overall study) and recent MI (22 %, similar to the overall). The arms do not appear as well balanced with regard to these factors. More of the Abciximab-low dose heparin patients had unstable angina (50 %), and more of the Abciximab standard dose heparin patients had a positive functional study (30 %). (see Table 7)

Table 7 Primary Indication for Index Intervention Among Angiographic Substudy Patients

	Total	Placebo + Std-Dose Heparin	Abciximab + Low-Dose Heparin	Abciximab + Std-Dose Heparin	Combined Abciximab Groups
Pts in Angiographic Substudy	286	95	102	89	191
Primary indication for intervention					
Unstable angina	120 (42.0%)	37 (38.9%)	51 (50.0%)	32 (36.0%)	83 (43.5%)
Chronic stable angina	25 (8.7%)	9 (9.5%)	8 (7.8%)	8 (9.0%)	16 (8.4%)
Recent myocardial infarction	62 (21.7%)	24 (25.3%)	20 (19.6%)	18 (20.2%)	38 (19.9%)
Positive functional study	70 (24.5%)	23 (24.2%)	20 (19.6%)	27 (30.3%)	47 (24.6%)
Other	9 (3.1%)	2 (2.1%)	3 (2.9%)	4 (4.5%)	7 (3.7%)

H. Cardiovascular Risk Factors

Overall, 17% of patients in the substudy had diabetes, less than in the overall study population (22 %). (see Table 8) Somewhat fewer patients in the substudy had hypertension compared to the overall (55 vs 59 %), and more substudy patients had a family history of premature CAD (56 vs 47 %).

Table 8 Cardiovascular Risk Factors Among Angiographic Substudy Patients

	Total	Placebo + Std-Dose Heparin	Abciximab + Low-Dose Heparin	Abciximab + Std-Dose Heparin	Combined Abciximab Groups
Pts in Angiographic Substudy	286	95	102	89	191
Diabetes	49 (17.2%)	14 (14.7%)	15 (14.9%)	20 (22.5%)	35 (18.4%)
Smoking					
Within past year	86 (30.1%)	32 (33.7%)	28 (27.5%)	26 (29.2%)	54 (28.3%)
Quit more than 1 year ago	106 (37.1%)	32 (33.7%)	38 (37.3%)	36 (40.4%)	74 (38.7%)
Never smoked	89 (31.1%)	30 (31.6%)	33 (32.4%)	26 (29.2%)	59 (30.9%)
Unknown	5 (1.7%)	1 (1.1%)	3 (2.9%)	1 (1.1%)	4 (2.1%)
Hypercholesterolemia	161 (61.0%)	50 (56.2%)	59 (62.8%)	52 (64.2%)	111 (63.4%)
Hypertension	158 (55.4%)	54 (56.8%)	55 (53.9%)	49 (55.7%)	104 (54.7%)
Family history of premature coronary artery disease	151 (55.5%)	52 (55.8%)	54 (53.1%)	44 (52.4%)	98 (52.7%)

I. Concomitant Medications--Heparin

The amount of heparin given during the procedure and the ACT values achieved were similar in the substudy to those in the overall study (see Table 9). A smaller proportion of patients in the substudy received post-procedure heparin in all treatment groups (20 to 27 %) than in the overall study. Substudy patients received less heparin post sheath removal also.

J. Other Medications

The use of cardiac medications was similar among substudy patients to the overall study. More substudy patients received ticlopidine (21 vs 14%); reflecting the larger proportion of substudy patients who were also in the STENT substudy.

Open label Abciximab was used during the 6 month study period in 1.4 % of patients in the overall study. In the substudy, 11 patients (3.8 %) received open label or commercial Abciximab during this period (see Table 10), 7 placebo, 1 Abciximab-low dose, and 3 Abciximab-standard dose heparin. For all 7 placebo patients, study agent was discontinued and Abciximab started within one hour. Two Abciximab plus standard dose heparin patients received commercial ReoPro between 30 days and 6 months post randomization.

Table 9 appears on the following two pages.

Table 10 Open-Label and Commercial Abciximab Use Between Study Entry and 6 Months Post Randomization Among Angiographic Substudy Patients

	Total	Placebo + Std-Dose Heparin	Abciximab + Low-Dose Heparin	Abciximab + Std-Dose Heparin	Combined Abciximab Groups
Pts in Angiographic Substudy	286	95	102	89	191
Pts receiving open-label or commercial abciximab	11 (3.8%)	7 (7.4%)	1 (1.0%)	3 (3.4%)	4 (2.1%)
Start of abciximab administration					
<1hr after end of study agent	8	7	0	1	1
≥1 hr after end of study agent to discharge	0	0	0	0	0
Discharge[a] to 30 days	0	0	0	0	0
30 days to 6 months	2	0	0	2	2
Not treated with study agent	1	0	1	0	1

[a] Or Day 7, whichever came first.

Table 9a. Heparin Administration and ACT Measurements Prior to and During the Index Intervention Among Angiographic Substudy Patients

	Total	Placebo + Std-Dose Heparin	Abciximab + Low-Dose Heparin	Abciximab + Std-Dose Heparin	Combined Abciximab Groups
Pts in Angiographic Substudy	286	95	102	89	191
Pts with PCI attempted	283	94	100	89	189
Pts receiving pre-cath lab heparin	110 (38.9%)	37 (39.4%)	40 (40.0%)	33 (37.1%)	73 (38.6%)
Total dose during procedure (U)					
n	280	94	97	89	186
Median	8600.0	11105.4	6000.0	8613.3	7000.0
Interquartile range	(6300.0, 11100.0)	(9500.0, 13637.5)	(4900.0, 7000.0)	(7800.0, 10169.2)	(5500.0, 9557.5)
Range	(210.0, 39700.0)	(4700.0, 39700.0)	(210.0, 14126.6)	(1600.0, 38600.0)	(210.0, 38600.0)
Total dose during procedure (U/kg)					
n	280	94	97	89	186
Median	100.0	147.2	71.0	101.4	85.0
Interquartile range	(73.1, 142.9)	(104.5, 169.5)	(67.8, 86.3)	(86.4, 122.2)	(70.1, 103.6)
Range	(2.3, 470.7)	(73.7, 300.8)	(2.3, 186.4)	(25.4, 470.7)	(2.3, 470.7)
Median ACT (sec)					
Pre-initial heparin[a]	131.0	135.0	128.0	134.0	130.0
Pre-device[b]	326.0	325.5	286.0	374.5	329.0
Minimum at or after device activation	304.0	313.0	265.0	333.0	301.5
Maximum during procedure[c]	341.0	342.5	300.5	387.5	341.0

[a] Last ACT prior to initial heparin bolus in cath lab
[b] Last ACT prior to first device activation
[c] Includes ACT pre-device activation.

Table 9b **Heparin Administration After Index Intervention Among Angiographic Substudy Patients**

	Total	Placebo + Std-Dose Heparin	Abciximab + Low-Dose Heparin	Abciximab + Std-Dose Heparin	Combined Abciximab Groups
Pts in Angiographic Substudy	286	95	102	89	191
Pts with PCI attempted	283	94	100	89	189
Pts receiving post-procedural heparin prior to sheath removal	67 (23.7%)	26 (27.7%)	23 (23.0%)	18 (20.2%)	41 (21.7%)
Duration					
<2 hours	5 (1.8%)	0 (0.0%)	3 (3.0%)	2 (2.2%)	5 (2.6%)
2-6 hours	15 (5.3%)	4 (4.3%)	7 (7.0%)	4 (4.5%)	11 (5.8%)
6-12 hours	8 (2.8%)	4 (4.3%)	3 (3.0%)	1 (1.1%)	4 (2.1%)
> 12 hours	32 (11.3%)	14 (14.9%)	7 (7.0%)	11 (12.4%)	18 (9.5%)
Unknown duration	7 (2.5%)	4 (4.3%)	3 (3.0%)	0 (0.0%)	3 (1.6%)
Dose (U)					
n	61	22	21	18	39
Median	8967.5	10876.7	3080.0	10742.5	7220.8
Interquartile range	(3000.0, 14277.6)	(6262.5, 15615.0)	(2056.3, 9882.3)	(4025.0, 15208.3)	(2251.1, 13600.0)
Range	(95.0, 31516.7)	(1750.0, 21608.4)	(642.8, 31516.7)	(95.0, 27380.8)	(95.0, 31516.7)
Pts receiving heparin after sheath removal	90 (31.8%)	34 (36.2%)	33 (33.0%)	23 (25.8%)	56 (29.6%)
Duration					
<12 hours	14 (4.9%)	5 (5.3%)	5 (5.0%)	4 (4.5%)	9 (4.8%)
12-24 hours	45 (15.9%)	14 (14.9%)	16 (16.0%)	15 (16.9%)	31 (16.4%)
>24 hours	29 (10.2%)	14 (14.9%)	11 (11.0%)	4 (4.5%)	15 (7.9%)
Unknown duration	2 (0.7%)	1 (1.1%)	1 (1.0%)	0 (0.0%)	1 (0.5%)

K. Index Intervention Characteristics

All but 3 substudy patient had intervention attempted. Seventy percent had balloon angioplasty only (compared to 78 % in the overall study). More substudy patients had either primary (8 vs 2 %) or bail out STENTS (15 vs 11 %) than the overall trial (see Table 11). Bail-out STENT use was lowest in the Abciximab-low dose heparin arm, as was the case in the overall trial. The median duration of the procedure was similar to that in the overall trial; however in the overall trial the procedure times were shorter in the Abciximab arms.

Most Abciximab Standard Dose Heparin patients had lesions in the LAD treated (54%), and more patients in the other two arms had RCA lesions (Table 12). The minimum pre-intervention TIMI grade was 3 in 70% of patients (a bit less in placebo patients). The maximum pre-intervention stenosis in any target lesion was 71 %, similar among groups,but the range was lower in the Abciximab-standard dose heparin arm (see Table 12).

Lesion characteristics as assessed by the Core Lab appear in Table 13. Imbalance in several characteristics is noted among the treatment arms; notably, more patients in the Abciximab Standard Dose treatment arm had a smooth contour, no side branches and absent thrombus compared with the other two arms.

Complications occurring during the index procedure appear in Table 14. Complications occurred in 52 % of substudy patients overall, including Type B dissection (a tear) in 36 %. The proportions were similar across treatment arms. The outcome was successful in all treated lesions in 76 % placebo patients, and in 80 % of the Abciximab - treated patients (both arms).

Reviewer Comment: Dissection during the procedure is a common factor which may change a patient thought to be low risk for ischemic complications at enrollment into a high risk patient. If dissection occurs in one-third of patients undergoing percutaneous intervention, that is a significant factor suggesting that predicting risk status prior to intervention may not be meaningful.

Table 11 Number of Angiographic Substudy Patients with Index Intervention Attempted and Intervention Characteristics

	Total	Placebo + Std-Dose Heparin	Abciximab + Low-Dose Heparin	Abciximab + Std-Dose Heparin	Combined Abciximab Groups
Pts in Angiographic Substudy	286	95	102	89	191
Pts with intervention attempted	283	94	100	89	189
Intervention type - all treated lesions[a]					
Balloon angioplasty	273 (96.5%)	90 (95.7%)	94 (94.0%)	89 (100.0%)	183 (96.8%)
Balloon only	200 (70.7%)	61 (64.9%)	75 (75.0%)	64 (71.9%)	139 (73.5%)
Directional atherectomy	7 (2.5%)	1 (1.1%)	4 (4.0%)	2 (2.2%)	6 (3.2%)
Rotational atherectomy	2 (0.7%)	0 (0.0%)	0 (0.0%)	2 (2.2%)	2 (1.1%)
TEC atherectomy	1 (0.4%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	1 (0.5%)
Laser	2 (0.7%)	2 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Randomized primary stent	23 (8.1%)	7 (7.4%)	8 (8.0%)	8 (9.0%)	16 (8.5%)
Bail-out stent	43 (15.2%)	19 (20.2%)	10 (10.0%)	14 (15.7%)	24 (12.7%)
Number of native vessels with lesions attempted					
0	7 (2.5%)	3 (3.2%)	3 (3.0%)	1 (1.1%)	4 (2.1%)
1	256 (90.5%)	87 (92.6%)	89 (89.0%)	80 (89.9%)	169 (89.4%)
2	20 (7.1%)	4 (4.3%)	8 (8.0%)	8 (9.0%)	16 (8.5%)
≥ 3	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pts with grafts attempted	7 (2.5%)	3 (3.2%)	3 (3.0%)	1 (1.1%)	4 (2.1%)
Number of segments attempted[b]					
1	214 (75.6%)	71 (75.5%)	76 (76.0%)	67 (75.3%)	143 (75.7%)
2	59 (20.8%)	21 (22.3%)	22 (22.0%)	16 (18.0%)	38 (20.1%)
≥ 3	10 (3.5%)	2 (2.1%)	2 (2.0%)	6 (6.7%)	8 (4.2%)
Duration of procedure (min)					
n	267	88	93	86	179
Median	31.0	28.5	38.0	31.0	33.0
Interquartile range	(17.0, 53.0)	(18.0, 58.5)	(17.0, 52.0)	(17.0, 53.0)	(17.0, 53.0)
Range	(2.0, 226.0)	(3.0, 169.0)	(2.0, 226.0)	(2.0, 187.0)	(2.0, 226.0)

[a] Some patients had more than one type of intervention.
[b] Includes grafts

Table 12 Number of Angiographic Substudy Patients by Number, Location, Minimum Pre-Intervention TIMI Grade and Maximum Pre-Intervention Stenosis of Lesions Evaluated During Index Intervention: Angiographic Core Laboratory Assessment

	Total	Placebo + Std-Dose Heparin	Abciximab + Low-Dose Heparin	Abciximab + Std-Dose Heparin	Combined Abciximab Groups
Pts in Angiographic Substudy	286	95	102	89	191
Pts with index angiograms evaluated by Core Lab	284	95	100	89	189
Vessels with lesions evaluated[a]					
LAD	117 (41.2%)	32 (33.7%)	54 (54.0%)	31 (34.8%)	85 (45.0%)
LCX	69 (24.3%)	25 (26.3%)	20 (20.0%)	24 (27.0%)	44 (23.3%)
RCA	107 (37.7%)	38 (40.0%)	31 (31.0%)	38 (42.7%)	69 (36.5%)
RCX	1 (0.4%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	1 (0.5%)
Ramus	4 (1.4%)	1 (1.1%)	0 (0.0%)	3 (3.4%)	3 (1.6%)
SVG	5 (1.8%)	2 (2.1%)	2 (2.0%)	1 (1.1%)	3 (1.6%)
LIMA	3 (1.1%)	1 (1.1%)	0 (0.0%)	2 (2.2%)	2 (1.1%)
Minimum pre-intervention TIMI grade in any target lesion[b]					
3	202 (71.1%)	64 (67.4%)	72 (72.0%)	66 (74.2%)	138 (73.0%)
2A	31 (10.9%)	13 (13.7%)	12 (12.0%)	6 (6.7%)	18 (9.5%)
2B	18 (6.3%)	3 (3.2%)	6 (6.0%)	9 (10.1%)	15 (7.9%)
2C	1 (0.4%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	1 (0.5%)
1	19 (6.7%)	8 (8.4%)	5 (5.0%)	6 (6.7%)	11 (5.8%)
0	13 (4.6%)	7 (7.4%)	4 (4.0%)	2 (2.2%)	6 (3.2%)
Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Maximum pre-intervention stenosis in any target lesion (%)					
n	279	93	98	88	186
Median	70.5	69.6	71.8	68.7	70.7
Interquartile range	(64.2, 76.9)	(63.5, 76.2)	(65.2, 78.9)	(62.9, 75.8)	(64.7, 76.9)
Range	(22.8, 100.0)	(42.2, 100.0)	(40.8, 100.0)	(22.8, 100.0)	(22.8, 100.0)

[a] Some patients are included in more than one category.
[b] See Attachment 4 for Angiographic Core Laboratory definitions.

Table 13 Number of Angiographic Substudy Patients by Baseline Angiographic Characteristics of Lesions Attempted During the Index Intervention: Angiographic Core Laboratory Assessment

	Total	Placebo + Std-Dose Heparin	Abciximab + Low-Dose Heparin	Abciximab + Std-Dose Heparin	Combined Abciximab Groups
Pts in Angiographic Substudy	286	95	102	89	191
Pts with index angiograms evaluated by Core Lab	284	95	100	89	189
Angiographic characteristics[a]					
Length					
<10 mm	87 (30.6%)	29 (30.5%)	34 (34.0%)	24 (27.0%)	58 (30.7%)
10-20 mm	135 (47.5%)	39 (41.1%)	47 (47.0%)	49 (55.1%)	96 (50.8%)
>20 mm	49 (17.3%)	20 (21.1%)	15 (15.0%)	14 (15.7%)	29 (15.3%)
Eccentricity					
Concentric	159 (56.0%)	55 (57.9%)	53 (53.0%)	51 (57.3%)	104 (55.0%)
Eccentric	111 (39.1%)	33 (34.7%)	42 (42.0%)	36 (40.4%)	78 (41.3%)
Proximal tortuosity					
None	154 (54.2%)	49 (51.6%)	59 (59.0%)	46 (51.7%)	105 (55.6%)
1-60°	81 (28.5%)	32 (33.7%)	22 (22.0%)	27 (30.3%)	49 (25.9%)
2-60° or 1-90°	45 (15.8%)	14 (14.7%)	18 (18.0%)	13 (14.6%)	31 (16.4%)
2 or more 90°	4 (1.4%)	0 (0.0%)	1 (1.0%)	3 (3.4%)	4 (2.1%)
Angulation					
<45°	237 (83.5%)	78 (82.1%)	84 (84.0%)	75 (84.3%)	159 (84.1%)
45° -60°	35 (12.3%)	11 (11.6%)	11 (11.0%)	13 (14.6%)	24 (12.7%)
>60°	5 (1.8%)	2 (2.1%)	2 (2.0%)	1 (1.1%)	3 (1.6%)
Contour					
Smooth	161 (56.7%)	44 (46.3%)	62 (62.0%)	55 (61.8%)	117 (61.9%)
Irregular	88 (31.0%)	32 (33.7%)	28 (28.0%)	28 (31.5%)	56 (29.6%)
Ulcerated	21 (7.4%)	11 (11.6%)	5 (5.0%)	5 (5.6%)	10 (5.3%)
Side branch					
None	108 (38.0%)	30 (31.6%)	39 (39.0%)	39 (43.8%)	78 (41.3%)
<2 mm	136 (47.9%)	51 (53.7%)	46 (46.0%)	39 (43.8%)	85 (45.0%)
>2 mm	21 (7.4%)	6 (6.3%)	7 (7.0%)	8 (9.0%)	15 (7.9%)
Analysis[b]	11 (3.9%)	3 (3.2%)	5 (5.0%)	3 (3.4%)	8 (4.2%)
Location					
Not ostial	243 (85.6%)	81 (85.3%)	90 (90.0%)	72 (80.9%)	162 (85.7%)
Ostial	41 (14.4%)	14 (14.7%)	10 (10.0%)	17 (19.1%)	27 (14.3%)
Local calcification					
None or mild	264 (93.0%)	86 (90.5%)	94 (94.0%)	84 (94.4%)	178 (94.2%)
Moderate to severe	17 (6.0%)	8 (8.4%)	5 (5.0%)	4 (4.5%)	9 (4.8%)
Thrombus					
Absent	67 (23.6%)	14 (14.7%)	27 (27.0%)	26 (29.2%)	53 (28.0%)
Low probability	110 (38.7%)	36 (37.9%)	42 (42.0%)	32 (36.0%)	74 (39.2%)
Possible	41 (14.4%)	15 (15.8%)	14 (14.0%)	12 (13.5%)	26 (13.8%)
Probable	23 (8.1%)	7 (7.4%)	9 (9.0%)	7 (7.9%)	16 (8.5%)
Definite	29 (10.2%)	15 (15.8%)	4 (4.0%)	10 (11.2%)	14 (7.4%)
Vessel occluded	13 (4.6%)	7 (7.4%)	4 (4.0%)	2 (2.2%)	6 (3.2%)

[a] For each characteristic, the most severe classification across all lesions attempted is counted. See Attachment 4 for Angiographic Core Laboratory morphology definitions.

[b] A side branch within an intervened lesion which is also intervened.

Table 14 Number of Angiographic Substudy Patients with Complications During Index Intervention and Type of Complications: Angiographic Core Laboratory Assessment

	Total	Placebo + Std-Dose Heparin	Abciximab + Low-Dose Heparin	Abciximab + Std-Dose Heparin	Combined Abciximab Groups
Pts in Angiographic Substudy	286	95	102	89	191
Patients with index angiograms evaluated by Core Lab	284	95	100	89	189
Angiographic outcome					
Successful in all treated lesions[a]	223 (78.5%)	72 (75.8%)	80 (80.0%)	71 (79.8%)	151 (79.9%)
Failed in at least one treated lesion	40 (14.1%)	14 (14.7%)	13 (13.0%)	13 (14.6%)	26 (13.8%)
Unknown outcome	18 (6.3%)	8 (8.4%)	5 (5.0%)	5 (5.6%)	10 (5.3%)
PCI not attempted	3 (1.1%)	1 (1.1%)	2 (2.0%)	0 (0.0%)	2 (1.1%)
Patients with complications	147 (51.8%)	50 (52.6%)	50 (50.0%)	47 (52.8%)	97 (51.3%)
% difference from placebo			-5.0%	0.3%	-2.5%
p-value vs placebo			1.000	1.000	1.000
Type of complication[b,c]					
Dissection morphology					
Type B	102 (35.9%)	31 (32.6%)	35 (35.0%)	36 (40.4%)	71 (37.6%)
Type C	16 (5.6%)	7 (7.4%)	6 (6.0%)	3 (3.4%)	9 (4.8%)
Type D	9 (3.2%)	2 (2.1%)	4 (4.0%)	3 (3.4%)	7 (3.7%)
Type E	4 (1.4%)	2 (2.1%)	0 (0.0%)	2 (2.2%)	2 (1.1%)
Type F	2 (0.7%)	1 (1.1%)	1 (1.0%)	0 (0.0%)	1 (0.5%)
Dissection length					
≤2 mm	38 (13.4%)	11 (11.6%)	14 (14.0%)	13 (14.6%)	27 (14.3%)
2-10 mm	83 (29.2%)	29 (30.5%)	27 (27.0%)	27 (30.3%)	54 (28.6%)
>10 mm	11 (3.9%)	3 (3.2%)	4 (4.0%)	4 (4.5%)	8 (4.2%)
Abrupt occlusion	10 (3.5%)	3 (3.2%)	3 (3.0%)	4 (4.5%)	7 (3.7%)
Thrombus					
Possible	2 (0.7%)	1 (1.1%)	0 (0.0%)	1 (1.1%)	1 (0.5%)
Probable	6 (2.1%)	2 (2.1%)	3 (3.0%)	1 (1.1%)	4 (2.1%)
Definite	7 (2.5%)	4 (4.2%)	1 (1.0%)	2 (2.2%)	3 (1.6%)
Vessel occluded	2 (0.7%)	1 (1.1%)	1 (1.0%)	0 (0.0%)	1 (0.5%)
Distal embolization	6 (2.1%)	3 (3.2%)	2 (2.0%)	1 (1.1%)	3 (1.6%)
Side branch occlusion	15 (5.3%)	8 (8.4%)	4 (4.0%)	3 (3.4%)	7 (3.7%)

[a] A successful intervention is defined as a residual stenosis ≤ 50%.
[b] Some patients had more than one complication.
[c] See Attachment 4 for Angiographic Core Laboratory morphology definitions.

Table 15 Minimum Luminal Diameter at Baseline, Post Procedure, and Follow Up: Angiographic Core Laboratory Assessment

	Placebo + Std-Dose Heparin	Abciximab + Low-Dose Heparin	Abciximab + Std-Dose Heparin	Combined Abciximab Groups
Pts in Angiographic Substudy	95	102	89	191
Pts with index and follow-up angiograms evaluated by Core Lab	74	85	73	158
Minimum luminal diameter (mm)[a]				
Baseline (preprocedure)				
n[b]	101 (73)	106 (82)	98 (73)	204 (155)
Mean ± SD	.88 ± .34	.80 ± .32	.85 ± .36	.82 ± .34
Median	.85	.78	.78	.78
Interquartile range	(.67, 1.07)	(.62, .96)	(.57, 1.05)	(.61, 1.02)
Range	(0, 2)	(0, 2.27)	(0, 2.31)	(0, 2.31)
Post procedure				
n[b]	101 (74)	110 (84)	100 (72)	210 (156)
Mean ± SD	1.75 ± .48	1.66 ± .49	1.70 ± .49	1.68 ± .48
Median	1.70	1.59	1.64	1.61
Interquartile range	(1.42, 1.94)	(1.33, 1.99)	(1.31, 2.07)	(1.32, 2.01)
Range	(.95, 3.23)	(.70, 3.15)	(.81, 3.05)	(.70, 3.15)
Follow up				
n[b]	99 (71)	106 (81)	98 (72)	204 (153)
Mean ± SD	1.35 ± .51	1.29 ± .58	1.34 ± .50	1.32 ± .54
Median	1.36	1.24	1.32	1.27
Interquartile range	(1.05, 1.61)	(.87, 1.62)	(.99, 1.63)	(.94, 1.62)
Range	(0, 2.7)	(0, 3.36)	(0, 3.11)	(0, 3.36)
ANOVA model				
Estimated mean ± SE	1.35 ± .06	1.30 ± .06	1.34 ± .06	1.32 ± .04
Treatment effect ± SE	-	-.04 ± .08	-.01 ± .08	-.03 ± .07
p-value	-	.581	.925	.713

[a] Distribution is based on average minimum luminal diameter across 2 views. If only one view has data, the value for the non-missing view is used in place of the average.

[b] Number of lesions (patients).

Table 16 Early Gain and Late Loss: Angiographic Core Laboratory Assessment

	Placebo + Std-Dose Heparin	Abciximab + Low-Dose Heparin	Abciximab + Std-Dose Heparin	Combined Abciximab Groups
Pts in Angiographic Substudy	95	102	89	191
Pts with index and follow-up angiograms evaluated by Core Lab	74	85	73	158
Early gain[a]				
n[b]	99 (73)	103 (80)	95 (72)	198 (152)
Mean ± SD	.89 ± .52	.87 ± .49	.87 ± .52	.87 ± .50
Median	.82	.80	.82	.81
Interquartile range	(.54, 1.23)	(.58, 1.21)	(.51, 1.24)	(.54, 1.21)
Range	(-.34, 2.38)	(-.19, 2.37)	(-.21, 2.00)	(-.21, 2.37)
ANOVA model				
Estimated mean ± SE	.91 ± .06	.92 ± .05	.90 ± .06	.91 ± .04
Treatment effect ± SE	-	.01 ± .08	-.01 ± .08	-.00 ± .07
p-value	-	.883	.881	.997
Late loss[a]				
n[b]	95 (70)	102 (78)	93 (70)	195 (148)
Mean ± SD	.40 ± .58	.35 ± .55	.37 ± .54	.36 ± .54
Median	.34	.37	.33	.37
Interquartile range	(-.01, .76)	(.01, .61)	(-.05, .66)	(-.03, .65)
Range	(-.80, 2.06)	(-.92, 2.29)	(-.41, 2.06)	(-.92, 2.29)
ANOVA model				
Estimated mean ± SE	.42 ± .06	.38 ± .06	.40 ± .06	.39 ± .04
Treatment effect ± SE	-	-.03 ± .09	-.02 ± .09	-.03 ± .07
p-value	-	.689	.813	.715

[a] Distribution is based on average across 2 views. If only one view has data, the value for the non-missing view is used in place of the average.

[b] Number of lesions (patients).

2. Early Gain and Late Loss – Early gain reflects the immediate increase in luminal diameter as a result of the procedure. Late loss reflects the loss in luminal diameter during the period from post-procedure through 6 months. No meaningful differences were observed among treatment groups on either of these parameters (see Table 16). The mean and median values were similar among treatment groups, although the range for both early gain and late loss was slightly smaller for the Abciximab Standard Dose Heparin arm compared to the other 2 arms. There was no discernable treatment effect by the sponsor's analysis using the ANOVA model.

3. Net Gain and Loss Index -- Net gain reflects the net gain in MLD over follow-up relative to the pre-treatment value, and is calculated by subtraction of the MLD prior to the procedure from the MLD at 6 months follow-up. The loss index reflects the loss in MLD over time relative to the initial gain, and is calculated as a ratio of (MLD post procedure - MLD at follow-up)/ (Mld post procedure - MLD pre-procedure). (A good result on the loss index will yield a number less than 1. A negative number will be obtained if the procedure was successful and the MLD at follow-up is even larger than the post-procedure value, or if the procedure was not successful). No significant differences were observed among treatment groups on this calculated value (see Table 17).

Reviewer's Note: The range of values is markedly different in the placebo arm compared to the Abciximab arms, and contains some negative values. The mean and median values are not different enough to yield significantly different results, however. The values for the Abciximab arms are quite similar on this parameter.

Table 17 Net Gain and Loss Index: Angiographic Core Laboratory Assessment

	Placebo + Std-Dose Heparin	Abciximab + Low-Dose Heparin	Abciximab + Std-Dose Heparin	Combined Abciximab Groups
Pts in Angiographic Substudy	95	102	89	191
Pts index and follow-up angiograms evaluated by Core Lab	74	85	73	158
Net gain[a]				
n[b]	95 (68)	101 (78)	93 (72)	194 (150)
Mean ± SD	.49 ± .54	.51 ± .54	.49 ± .55	.50 ± .54
Median	.48	.45	.41	.44
Interquartile range	(.17, .79)	(.16, .83)	(.15, .81)	(.15, .82)
Range	(-.83, 2.15)	(-.73, 2.28)	(-1.0, 1.91)	(-1.0, 2.28)
ANOVA model				
Estimated mean ± SE	.50 ± .06	.51 ± .06	.49 ± .06	.50 ± .04
Treatment effect ± SE	-	.01 ± .08	-.01 ± .08	.01 ± .07
p-value	-	.846	.952	.940
Loss index[a]				
n[b]	90 (66)	93 (75)	89 (70)	182 (145)
Mean ± SD	-.14 ± 4.3	.34 ± 1.00	.22 ± 1.47	.28, 1.25
Median	.39	.49	.47	.48
Interquartile range	(-.02, .75)	(.10, .76)	(-.07, .78)	(-.04, .76)
Range	(-38, 3.6)	(-4.6, 3.0)	(-8.9, 2.7)	(-8.9, 3.0)
ANOVA model				
Estimated mean ± SE	.07 ± .26	.37 ± .26	.23 ± .26	.30 ± .19
Treatment effect ± SE	-	.44 ± .37	.29 ± .37	.36 ± .32
p-value	-	.235	.435	.257

[a] Distribution is based on average across 2 views. If only one view has data, the value for the non-missing

4. Percent Diameter Stenosis -- The means for this parameter were similar in all treatment groups at baseline, post procedure, and at followup. Standard deviations and ranges were mildly different, but there was no discernable treatment effect using the ANOVA model (see Table 18).

Table 18 Percent Diameter Stenosis: Angiographic Core Laboratory Assessment

	Placebo + Std-Dose Heparin	Abciximab + Low-Dose Heparin	Abciximab + Std-Dose Heparin	Combined Abciximab Groups
Pts in Angiographic Substudy	95	102	89	191
Pts with index and follow-up angiograms evaluated by Core Lab	74	85	73	158
Percent diameter stenosis[a]				
Baseline (preprocedure)				
n[b]	100 (72)	106 (83)	97 (72)	203 (155)
Mean ± SD	65.2 ± 12.9	69.1 ± 13.5	64.3 ± 14.9	66.8 ± 14.4
Median	65.8	69.3	66.1	68.3
Interquartile range	(57.8, 72.6)	(59.7, 76.8)	(56.4, 74.8)	(58.6, 75.8)
Range	(28.1, 100.0)	(30.6, 100.0)	(22.8, 100.0)	(22.8, 100.0)
Post procedure				
n[b]	99 (72)	109 (83)	101 (71)	210 (154)
Mean ± SD	31.1 ± 15.1	35.0 ± 12.7	32.1 ± 13.4	33.6 ± 13.1
Median	33.7	35.8	32.6	33.8
Interquartile range	(22.9, 38.8)	(26.4, 43.2)	(23.8, 40.9)	(24.4, 42.9)
Range	(-30.8, 70.4)	(2.1, 79.3)	(-3.2, 64.9)	(-3.2, 79.3)
Follow up				
n[b]	97 (71)	105 (81)	95 (71)	200 (152)
Mean ± SD	47.9 ± 18.4	49.8 ± 20.1	47.8 ± 16.7	48.9 ± 18.6
Median	49.4	51.3	47.0	48.5
Interquartile range	(35.6, 57.5)	(34.0, 64.3)	(34.6, 59.6)	(34.3, 61.8)
Range	(8.8, 100.0)	(11.2, 100.0)	(13.0, 100.0)	(11.2, 100.0)
ANOVA model				
Estimated mean ± SE	48.3 ± 2.0	49.8 ± 1.9	47.9 ± 2.0	48.9 ± 1.4
Treatment effect ± SE	-	1.6 ± 2.8	-0.4 ± 2.8	0.6 ± 2.4
p-value	-	.572	.899	.805
Lesions with restenosis (>50%)	46 (47%)	54 (51%)	43 (45%)	97 (49%)

[a] Distribution is based on average stenosis across 2 views. If only one view has data, the value for the non-missing view is used in place of the average.

[b] Number of lesions (patients).

IV. Results

A. Quantitative Angiographic Variables

1. Minimum Luminal Diameter (MLD) Abciximab had no significant effect on MLD during the study follow-up period (median values, standard deviation and range of values similar among treatment groups both post-procedure and at follow-up; see Table 15). There was no difference when STENT patients were excluded from the analysis.

   The results are displayed graphically in Figure 1.

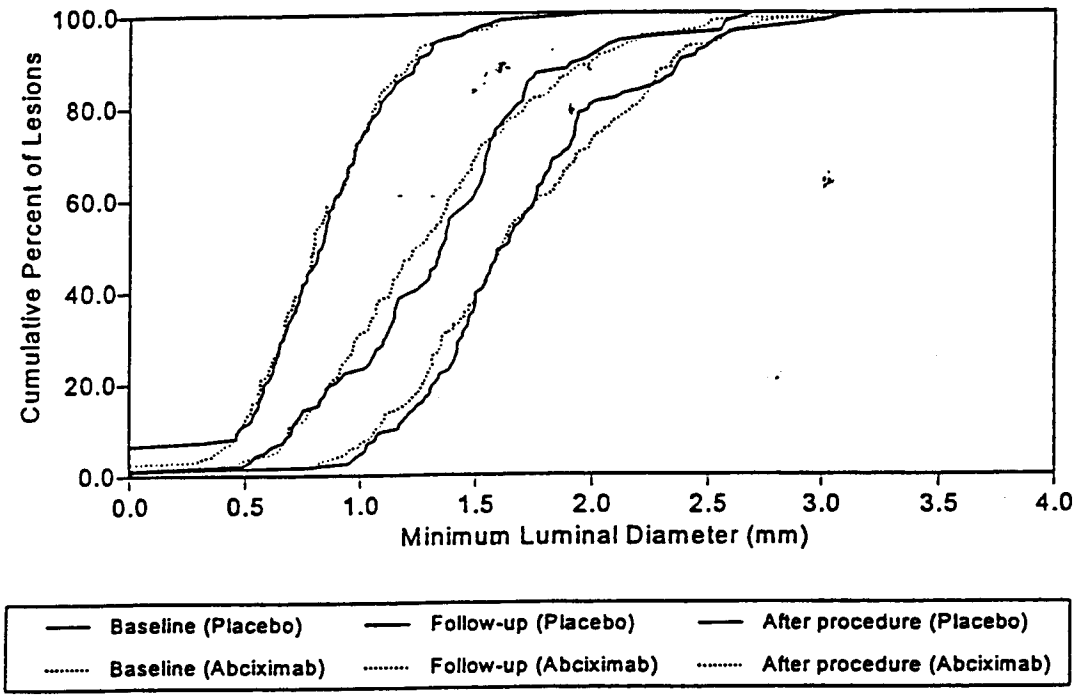

Figure 1 **Minimum Luminal Diameter (mm) at Baseline, Immediately Post Intervention, and at Follow Up. The pair of lines to the left represent baseline values, those in the middle represent follow-up values, and those to the right represent values immediately post intervention.**

B. Primary Clinical Endpoints

Angiographic Substudy patients had modestly higher event rates than were seen in the overall trial; however the magnitude of reductions in Abciximab treated patients compared to placebo are consistent with the results of the overall trial. Trends toward substantial reduction of the composites including death and MI and death, MI and urgent revascularization are seen in the Abciximab arms compared with placebo (see Table 19). Of interest, a significant reduction in the composite including death, MI or repeat revascularization at 6 months is seen in the patients in the Abciximab Standard Dose heparin arm compared to placebo. Patients in the Abciximab Low Dose Heparin group showed no real difference on this endpoint compared to placebo, as was the case for the overall trial.

Table 19 Primary Efficacy Endpoint Events among Angiographic Substudy Patients

	Total	Placebo + Std-Dose Heparin	Abciximab + Low-Dose Heparin	Abciximab + Std-Dose Heparin	Combined Abciximab Groups
Pts in Angiographic Substudy	286	95	102	89	191
Pts with death or MI at 30 days	24 (8.4%)	12 (12.7%)	7 (6.9%)	5 (5.6%)	12 (6.3%)
% change vs placebo			-46.0%	-55.8%	-50.6%
p-value			0.0871	0.0555	0.0360
Pts with death, MI, or urgent revascularization at 30 days	27 (9.5%)	14 (14.8%)	8 (7.8%)	5 (5.6%)	13 (6.8%)
% change vs placebo			-47.1%	-62.1%	-54.1%
p-value			0.0646	0.0244	0.0167
Pts with death, MI, or repeat revascularization at 6 months	64 (22.5%)	25 (26.3%)	26 (25.6%)	13 (14.7%)	39 (20.5%)
% change vs placebo			-2.9%	-44.1%	-22.0%
p-value			0.3825	0.0239	0.1047

C. Secondary Clinical Endpoints

Secondary endpoint events included clinical events in the angiographic substudy patients. Trends appear consistent with the overall trial results in the placebo and Abciximab Low Dose Heparin arms (see Table 20). Here also, the Abciximab Standard Dose Heparin patients appeared to have fared better at 6 months compared to placebo than did the Abciximab Standard Dose patients. The Abciximab Standard Dose patients experienced significantly lower event rates than patients in the placebo arm on the composite including death, MI, and target vessel revascularization at 6 months. Trends showed substantially lower rates of death and MI and death, MI and urgent revascularization at 6 months, as well as target vessel revascularization, in patients in the Abciximab standard Dose arm compared to placebo.

Table 20 Secondary Efficacy Endpoint Events among Angiographic Substudy Patients

	Total	Placebo + Std-Dose Heparin	Abciximab + Low-Dose Heparin	Abciximab + Std-Dose Heparin	Combined Abciximab Groups
Pts in Angiographic Substudy	286	95	102	89	191
Pts with death or MI at 6 months	26 (9.1%)	12 (12.6%)	9 (8.9%)	5 (5.6%)	14 (7.4%)
% change vs placebo			-29.5%	-55.5%	-41.5%
p-value			0.187	0.055	0.071
Pts with death, MI, urgent revascularization at 6 months	35 (12.3%)	15 (15.8%)	13 (12.8%)	7 (7.9%)	20 (10.5%)
% change vs placebo			-18.8%	-50.0%	-33.2%
p-value			0.252	0.052	0.093
Pts with death, MI, TVR at 6 months	61 (21.4%)	25 (26.3%)	25 (24.6%)	11 (12.4%)	36 (19.0%)
% change vs placebo			-6.6%	-52.7%	-28.0%
p-value			0.324	0.009	0.058
Pts with TVR at 6 months	46 (16.2%)	17 (17.9%)	20 (19.7%)	9 (10.3%)	29 (15.4%)
% change vs placebo			9.9%	-42.6%	-14.2%
p-value			0.398	0.072	0.280

Reviewer's Comment: It is not clear what the factors are contributing to the results demonstrating a more substantial benefit in the Abciximab Standard Dose Heparin patients at 6 months.

V. Sponsor's Conclusions

Despite reductions in clinical endpoints among substudy patients in the Abciximab arms at both 30 days and 6 months, no differences were observed in quantitative angiographic variables. The sponsor notes that given the small number of patients enrolled in the substudy prior to the early termination of the main trial, there was low statistical power to detect the anticipated 15 % reduction in minimum luminal diameter. They comment that the ongoing EPILOG STENT Study may provide a more meaningful assessment of the effect of Abciximab on angiographic restenosis.

VI. Reviewer's Conclusions

This reviewer agrees that the small sample size in this study led to a reduced power to detect a meaningful difference in angiographic parameters among treatment arms. It is interesting that clinical benefit is seen in the Abciximab treated patients in this study, but the angiographic results are truly equivocal.

One of the reviewer's questions in reviewing these data was whether the "catch up" in total revascularization procedures seen among Abciximab treated patients compared to the placebo arm over the 6 month follow-up had any physiologic correlates discernable by the angiographic parameters measured in this study. The fact that there were no meaningful 6 month angiographically demonstrable benefits in Abciximab-treated patients at 6 months is consistent with the hypothesis that Abciximab does not retard the process of atherosclerosis. This may be the reason for the equivalent number of total revascularization procedures seen among treatment arms at 6 months, despite a persistent reduction in urgent procedures. The data do not definitively establish this as the reason, however. Nor do the results of this substudy do not show any evidence of a negative effect of Abciximab that might be responsible.

A surprising finding from this substudy is the reduced incidence of clinical endpoints in the Abcximab Standard Dose Heparin arm compared to the other 2 treatment arms, both at 30 days and at 6 months. Many mild imbalances are evident in the characteristics of patients in this group compared to the other 2 groups. Perhaps those factors are responsible for the selection of an atypical sample in this substudy. Or perhaps the group selected represents a subgroup of patients who actually benefitted more from the combination of Abciximab with standard dose heparin.

Overall, the Angiographic Substudy results do not demonstrate any meaningful differences in 6 month angiographic outcomes between patients treated with placebo and those treated with Abciximab.

5.0 THE READMINISTRATION STUDY

I. Study Synopsis

This review concerns an open label protocol examining the effects of injection and reinjection of Abciximab after 14 weeks on healthy volunteer subjects and patients with stable coronary artery disease. Pharmacokinetics of Abciximab distribution and clearance, and pharmacodynamic effects on binding to platelets were examined, as well as immune responses to the antibody and adverse events were recorded. Effects on all these parameters were examined for the first injection as well as for the reinjection, and these results were compared.

A separate review of the PK and PD aspects of the study is provided by the Pharmacology Reviewer. No issues have been raised by that reviewer regarding the sponsor's following conclusions:

- The pharmacokinetic assessments on the first and the second administration suggest comparable rates of clearance.

- Both platelet aggregation and quantitative measurements of GP IIb/IIIa receptor blockade indicate similar anti-platelet effects following the first and the second treatments.

- No differences were seen in the duration of or distribution of platelet bound Abciximab following the first and the second treatments. Platelet bound Abciximab was detected in the circulation for 15 days in most patients.

The Pharmacology reviewer notes that there was a large individual variability in pharmacokinetics, but there were no differences notable between weight or dosage groups. That is, the weight adjusted and the non weight adjusted regimens had generally the same kinetics. That reviewer also noted that the percent inhibition of platelet aggregation appeared quite constant at between 80 and 100 % over wide variances in Abciximab levels throughout the infusion times. Quite consistently, the inhibition of aggregation was maintained throughout the infusion and was restored gradually over the hours and days following the injections. By 3 days, there was a substantial return of function seen, though Abciximab remained in the circulation for up to 15 days.

This review will address the immune responses, bleeding, thrombocytopenia and the effect on clotting parameters reported in the study.

II. Protocol and Amendments (originally submitted October 1994; trial dates October 24, 1994 to January 30, 1995)

A. Objectives

To determine the immune response and safety profile of patients receiving a repeat injection of Abciximab, and to evaluate the *in vivo* biologic activity and pharmacokinetics of Abciximab.

B. Study Design

Open label single center single dose injection (bolus 0.25 mg/kg and 12 hour infusion, either 10 ug/min or 0.125 ug/kg/min), followed by reinjection with the same dose at 14 weeks if HACA negative through 12 weeks followup. *(Reviewer's Note: The protocol specified that patients with a positive HACA at 12 weeks would not be reinjected. In actual practice, patients with a positive HACA or HAMA at any time during the 12 weeks were not reinjected.)*

C. Patients

Planned to enroll —, (actually 41) male and female, ages 21-80, with documented coronary artery disease (amended to allow volunteers without CAD to be enrolled in December 1994). Patients were paid for participating.

D. Inclusion/Exclusion Criteria

• Included subjects with stable coronary artery disease, defined by: prior acute MI, angiogram with ≥ 50% narrowing of ≥ 1 coronary artery, or history of angina documented in medical records.

• Amended to include healthy volunteers when enrollment of stable CAD patients was slow.

• Excluded patients with potential increased risk for bleeding, on anticoagulants, elevated baseline PT, allergy to aspirin or murine proteins or have participated in a trial with murine or chimeric mAb, vasculitis, immune system disease, unstable cardiac patients, or arterial puncture in noncompressible site within 6 weeks prior to enrollment.

E. Treatment Groups

Subjects were randomized to receive either a weight adjusted (0.25 ug/kg/min) or a non weight adjusted (10 ug/min) 12 hour infusion, stratified by weight group and age ≤ 60 years, as follows:

Weight < 70 kg:	8 patients each weight adjusted and non weight adjusted infusion
Weight ≥ 70 kg, < 80 kg:	8 patients each weight adjusted and non weight adjusted infusion
Weight ≥ 80 kg:	8 patients non weight adjusted infusion

(note: all patients ≥ 80 kg received non-weight adjusted infusions in the EPILOG trial)

Reinjection was performed in the same manner. Each patient was reinjected with the same regimen as received the first time.

F. Concomitant Medications

Aspirin 325 mg po was given between 4 and 24 hrs prior to the abciximab.
(Heparin was not used).

G. Precautions

Drugs for treatment of allergic reactions, including epinephrine, dopamine, theophylline, and corticosteroids were available for immediate use in the event of an allergic or anaphylactic reaction. The infusion was to be stopped if symptoms suggestive of an allergic reaction appeared.

H. Procedures

After screening and baseline laboratory assessments, patients received the first bolus and injection intravenously and were observed for 24 hours. Vital signs were recorded and blood was taken for CBC, serum chemistries, PT, PTT, platelet counts, platelet aggregation, flow cytometry, assay of GPIIb/IIIa receptor blockade, and plasma Abciximab concentration at appropriate intervals. Amendments were added to determine if Abciximab has anticoagulant properties in addition to its antiplatelet effects; AT III and fibrinopeptide A levels were measured to assess the state of thrombin generation, and comparison of platelet aggregation in PRP and whole blood, and ACT in 20 patients. IgG recruitment to platelets was assessed by FACS analysis. Platelet counts were obtained at one hour

after injection and daily through 7 days post injection. A 24 hour urine collection was obtained to assess creatinine clearance and urinary excretion of Abciximab. All data were recorded in the same manner and at the same timepoints following the second injection.

History and physical were performed at screening and prior to reinjection. Patients were also examined 30 days following each injection at a repeat visit. History of adverse events and medication use were recorded. Any bleeding was identified by type, location, and onset date.

HACA and HAMA measurements were collected at baseline, 24 hours, 1, 2, 4, 8, and 12 weeks. Subjects who were HACA and HAMA negative were reinjected at 14 weeks. Subjects who were HACA or HAMA positive at any time were not re-injected.

(Reviewer's Note: The protocol specified that patients with a positive HACA at 12 weeks would not be reinjected. Subject ——— who had a low titer (1/40) positive HAMA at 8 weeks after the first injection, had readministration and developed thrombocytopenia. It was thought by the investigator that the low level immune response to the first injection may have contributed to the thrombocytopenia after the second. After that point, patients with a positive HACA or HAMA at any time during the 12 week followup after the first injection were not reinjected.)

Subjects with a positive HACA had HACA measurements made monthly for 4 months then every 3 months until negative. Enzyme immunoassays were used. The sample with peak reactivity from each patient was titered to quantify the response. Neutralization was required to confirm positive responses.

I. Statistics

No prospective hypothesis was stated. Descriptive statistics were used to analyze continuous variables, and categorical data were given by counts and percentages. Nonparametric rank based tests were used to examine changes in platelet counts and clearance of platelet-bound Abciximab. Correlation analysis was used to examine the relationship between variables. The effects of weight adjusted infusion dosing were examined using Fisher's exact test.

III. Study Results

A. Patient Disposition

Forty-one subjects were actually enrolled and received the initial injection. The distribution of subjects is shown in Table 1.

Table 1
DISTRIBUTION OF SUBJECTS

		Body Weight				
	Total	≤70 kg		70 to 80 kg		> 80 k
		Wt-Adj	Non-Wt-Adj	Wt-Adj	Non-Wt-Adj	Non-Wt-Adj
No. of Subjects						
Initial injection	41	9	8	8	8	8
Reinjection	29	7	3	6	5	8

Wt-Adj 0.25 mg/kg bolus plus weight-adjusted infusion (0.125 µg/kg/min)
Non-Wt-adj 0.25 mg/kg bolus plus non-weight-adjusted infusion (10 µg/min)

Twenty-nine subjects received the second injection. Twelve subjects were not reinjected; the reasons are shown in Table 2.

Table 2
SUBJECTS NOT REINJECTED WITH ABCIXIMAB

Subject	Reason
	HACA positive after first injection
	Positive immune response based on HAMA assay
	Positive immune response based on HAMA assay
	Carotid artery surgery 14 weeks after first injection
	Thrombocytopenia after first injection
	HACA positive after first injection
	HACA positive after first injection
	HACA positive after first injection
	HACA positive after first injection
	Positive immune response based on HAMA assay
	Positive immune response based on HAMA assay
	Withdrew consent

B. Discontinuation of Study Agent
All subjects received the full first bolus and infusion. Of the 29 subjects reinjected, one had the infusion discontinued after 9 hours due to the development of thrombocytopenia. All others received the full bolus and infusion.

C. Demographics
The demographic characteristics of all subjects enrolled are presented in Table 3, and subjects who were reinjected in Table 4 (following 2 pages). The mean age of all subjects was 62.9 years; the range was 43 to 79. Patients were stratified by weight group. Initially, patients with CAD were enrolled into the study; these were predominantly men, who predominantly fell into the 70 to 80 kg and over 80 kg groups. After the protocol was amended to allow healthy volunteers, more women (who were mostly less than 70 kg) were enrolled. There are no important differences between the group initially injected and the group reinjected on demographic characteristics.

D. Medical History

Fifty-eight percent of the subjects enrolled had a history of CAD. Eighty percent of the subjects had a family history of cardiovascular disease, 17 % had a history of hypertension, 1 subject had a history of IDDM, 4 prior CHF, and 10 subjects (22 %) had a history of prior cardiovascular events. The incidence of these was well balanced across treatment groups. Eight subjects (20%) had a prior PTCA and 4 had a prior CABG. None of the subjects had received Abciximab previously.

E. Concomitant Medications

A variety of medications was being taken by patients enrolled in the study, largely cardiac medications (see Table 5 on 3rd page following). Aspirin was frequently used, but no anti-platelet medications were allowed within 7 days prior to either injection and oral anticoagulants were allowed but not within 3 days prior to either injection.

Table 3

PATIENT DEMOGRAPHICS - ALL SUBJECTS ENROLLED

		Body Weight				
	Total	≤ 70 kg		70 to 80 kg		≥ 80 kg
		Wt-Adj	Non-Wt-Adj	Wt-Adj	Non-Wt-Adj	Non-Wt-Adj
	(n=41)	(n=9)	(n=8)	(n=8)	(n=8)	(n=8)
Age (yrs)						
Mean ± SD	62.9±10.0	60.2±11.8	64.1±10.6	62.9±9.5	63.9±9.9	63.8±10.0
Median	65	58	62	65	67	64
Range	43,79	45,74	51,78	49,74	46,73	43,79
Weight (kg)						
Mean ± SD	72.0±13.8	57.8±10.2	62.1±4.4	74.9±2.4	74.8±3.6	92.0±8.9
Median	72	63	62	75	76	89
Range	46,106	46,69	56,69	72,79	70,79	81,106
Height (cm)						
Mean ± SD	169.3±8.4	163.8±9.7	163.9±4.4	173.0±8.7	170.5±4.5	176.2±6.2
Median	170	165	165	172	170	176
Range	151,188	151,183	158,170	158,188	164,178	165,185
Race						
White	37 (90%)	9 (100%)	8 (100%)	7 (88%)	6 (75%)	7 (88%)
Black	3 (7%)	0	0	1 (12%)	2 (25%)	0
Other	1 (2%)	0	0	0	0	1 (12%)
Gender						
Female	17 (42%)	5 (56%)	7 (88%)	2 (25%)	3 (38%)	0
Male	24 (58%)	4 (44%)	1 (12%)	6 (75%)	5 (62%)	8 (100%)
History of CAD	24 (58%)	2 (22%)	2 (25%)	5 (62%)	7 (88%)	8 (100%)

Table 4

PATIENT DEMOGRAPHICS - SUBJECTS WHO WERE REINJECTED

		Body Weight				
	Total	≤ 70 kg		70 to 80 kg		≥ 80 kg
		Wt-adj	Non-Wt-Adj	Wt-Adj	Non-Wt-Adj	Non-Wt-Adj
	(n=29)	(n=7)	(n=3)	(n=6)	(n=5)	(n=8)
Age (yrs)						
Mean ± SD	61.8±10.3	58.7±12.5	63.3±13.7	59.3±8.2	64.8±10.8	63.8±10.0
Median	65	54	61	62	67	64
Range	43,79	45,74	51,78	49,68	46,73	43,79
Weight (kg) at Initial Injection						
Mean ± SD	74.4±14.7	58.7±10.5	61.7±2.1	74.8±2.8	75.2±3.9	92.1±8.9
Median	74	64	61	74	77	89
Range	46,106	46,69	60,64	72,79	71,79	81,106
Weight (kg) at Reinjection						
Mean ± SD	76.8±15.1	61.1±11.9	63.0±4.6	79.0±5.5	76.0±3.9	94.6±7.9
Median	77	67	62	78	77	92
Range	47,106	47,72	59,68	72,87	71,80	85,106
Height (cm)						
Mean ± SD	171.9±7.8	166.8±8.6	165.1±5.1	176.1±6.8	170.9±5.9	176.2±6.2
Median	173	165	165	175	173	176
Range	158,188	158,183	160,170	170,188	164,178	165,185
Race						
White	27 (93%)	7 (100%)	3 (100%)	6 (100%)	4 (80%)	7 (88%)
Black	1 (3%)	0	0	0	1 (20%)	0
Other	1 (3%)	0	0	0	0	1 (12%)
Gender						
Female	8 (28%)	3 (43%)	2 (67%)	1 (17%)	2 (40%)	0
Male	21 (72%)	4 (57%)	1 (33%)	5 (83%)	3 (60%)	8 (100%)
History of CAD	20 (69%)	2 (29%)	1 (33%)	4 (67%)	5 (100%)	8 (100%)

Table 5

MEDICATIONS ADMINISTERED WITHIN 7 DAYS PRIOR TO ABCIXIMAB INJECTION

	Total	Body Weight ≤ 70 kg		70 to 80 kg		> 80 kg
		Wt-Adj	Non-Wt-Adj	Wt-Adj	Non-Wt-Adj	Non-Wt-Adj
Initial Injection	(n=41)	(n=9)	(n=8)	(n=8)	(n=8)	(n=8)
Beta blocker	12 (29%)	0	3	3	1	5
Calcium channel blocker	10 (24%)	0	1	1	3	5
Nitrates	13 (32%)	2	1	0	3	7
Cardiac glycoside	1 (2%)	0	0	0	1	0
Oral anticoagulants	0	0	0	0	0	0
ACE inhibitor	1 (2%)	0	0	0	1	0
Diuretics	3 (7%)	1	0	0	1	1
Other antihypertensive	1 (2%)	1	0	0	0	0
Insulin	1 (2%)	0	0	0	1	0
Lipid lowering agent	4 (10%)	0	0	0	3	1
Aspirin[1]	21 (51%)	2	3	4	7	5
Reinjection	(n=29)	(n=7)	(n=3)	(n=6)	(n=5)	(n=8)
Beta blocker	7 (24%)	0	1	2	0	4
Calcium channel blocker	10 (34%)	0	1	1	2	6
Nitrates	8 (28%)	2	0	0	2	4
Cardiac glycoside	0	0	0	0	0	0
Oral anticoagulants	0	0	0	0	0	0
ACE inhibitor	0	0	0	0	0	0
Diuretics	2 (7%)	1	0	0	0	1
Other antihypertensive	1 (3%)	1	0	0	0	0
Insulin	0	0	0	0	0	0
Lipid lowering agent	4 (14%)	0	0	0	3	1
Aspirin[1]	17 (59%)	2	2	3	5	5

[1] Does not include protocol-mandated aspirin administered 4 to 24 hours prior to bolus administration

III. Immune Responses

HACA and HAMA antibody titers were measured at 1,2,4,8, and 12 weeks, and every 3 months thereafter to 15 months post injection or, if positive, monthly for four months then every 3 months until samples were negative.

A. Immune Responses - First Injection

After the first injection, 5 subjects (12 %) developed a positive HACA within 12 weeks. The onset in most was at 4 to 8 weeks; 1 subject became positive at 2 weeks. Two additional subjects became positive at 4 and 6 months after injection. Table 6 shows the subjects with positive titers, when they first developed, the peak titer observed, and the duration of positive responses.

Table 6 HACA Responses After First Injection

Subject #	Time First Positive	Peak Titer	Time to First Negative
-	4 weeks	1/400	7 months
—	4 weeks	1/50	12 weeks
—	2 weeks	1/800	15 months
—	8 weeks[1]	1/400	--[2]
—	4 weeks	1/800	--[2]
—	6 months	1/200	9 months
—	4 months	1/100	9 months

1 Reactive to 7E3 variable region at baseline
2 Still positive at last follow-up at 9 months
3 Also had an early positive HAMA

All 5 of the subjects who were HACA positive within the first 12 weeks developed positive HAMA responses also. A total of 10 subjects (25 %) developed positive HAMA responses. Two subjects who had an early positive HAMA low titer later developed positive HACA (— and — in Table 6 above). There were more low titers among the HAMA responses, as the assay was more sensitive than the HACA assay. Five of the 10 who had a HAMA response were still HAMA positive at 8 to 9 months; one subject was still positive at 18 months.

Note that 8 subjects (20 %) had positive HACA results at baseline (prior to treatment). Five of these subjects showed a > 50 % decrease in signal at 24 hours after treatment with Abciximab, suggesting a possible immune complex consumption of the HACA antibodies. None of the subjects were noted to experience any clinically apparent effects of such a phenomenon, however. All patients showed a similar pharmacodynamic profile to patients who did not have HACA positive titers at baseline.

B. Immune Responses - Second Injection

Following reinjection, a greater proportion of subjects developed positive HACA responses, and the onset was typically earlier than occurred after the first injection. Seven subjects (24 %) became positive after reinjection; 2 had detectable HACA at 1 week and 4 were positive by 2 weeks after reinjection. Titers ranged from 1:50 to 1:6400. No correlation was seen with any particular weight or dose group. Table 7 shows the positive responses after reinjection and when they developed. All were still positive at 12 weeks, and 3 of the 7 were still positive at 12 to 15 months).

Subject —— had a low titer positive HAMA after the first injection, and developed thrombocytopenia which was thought to be immune mediated after the second injection, and a positive HACA titer.

Table 7 HACA Responses After Second Injection

Subject #	Time First Positive	Peak Titer	Time to First Negative
——	4 weeks	1/200	8 months
——	2 weeks	1/400	--[1]
——	1 week	1/6400	--[2]
——	1 week	1/400	15 months[3]
——	4 weeks	1/50	7 months
——	12 weeks	1/50	10 months[4]
——	2 weeks	1/3200	--[5]

1 Positive at last follow-up (12 weeks)
2 Positive at last follow-up (15 months)
3 No data between 7 months (pos) and 15 months (neg)
4 No data between 4 months (pos) and 19 months (neg)
5 Positive at last follow-up (12 months)

Nine subjects developed HAMA responses after reinjection; all 7 of those who developed positive HACA, and 2 others. Titers ranged from 1:20 to 1:10,240. Seven of the nine were still positive at last followup at 12 to 15 months, and 2 were lost to followup.

There were two subjects who had a borderline positive HAMA response after the first injection who underwent reinjection, and had no clinical consequences (—— and ——. Subject —— developed a positive HACA after the second injection (Table 7 above).

IV. Clinical Consequences

A. Allergic and Anaphylactic Reactions

There were no reports of allergic or anaphylactic reactions after injection or reinjection in the study. One subject in the reinjection cohort (—— had thrombocytopenia which was thought to be immune-mediated due to a coincident rise in HACA titer. There was no evidence in the reinjected patients of accelerated clearance of Abciximab or of diminished receptor blockade or reduced inhibition of platelet aggregation that would have indicated immune consumption.

One subject had a facial dermatitis at 6 weeks after the initial injection and also noted after reinjection. That subject developed positive HAMA and HACA titers at 4 weeks after reinjection; no antibodies were detected after the first injection.

B. Thrombocytopenia
One case was seen during the first infusion:

Patient ——— - Baseline 224,000. Platelets decreased to 78,000 @ 30 minutes post bolus, - — was 2,000 at 12 hrs. Steady recovery was noted after 24 hrs by 20,000 per day to 139,000 on day 6, and back to baseline at 236,000 at 4 weeks. No bleeding.

Mechanism uncertain. Note that this patient was one who had a + HACA @ baseline, but all 4 other patients who were + at baseline had no adverse events recorded.

Reviewer Comment: It is possible that immune consumption played a role in the thrombocytopenia; the investigator and sponsor did not consider this evidence of an immune mechanism.

One case was seen during the second infusion:

Patient ——— - Baseline 170,000. Platelets 53,000 @ 9 hrs after 2nd injection; the infusion was stopped early. Platelets 67,000 @ 24 hrs, 90,000 @ 3 days, then 37,000 @ 8 days, 94,000 @ 11 days, stable at baseline by 2 and 4 weeks.

This patient was HACA + at 8 days after the reinjection. The investigator thought the platelet decrease was immune mediated, and definitely related to study agent. (The sponsor notes this patient had a + EIA @ baseline, and this obscured the probable immune response after the first injection.The neutralization profile showed an increasing proportion of serum antibodies reactive with the murine variable region to 21% at 4 weeks after the initial injection.)

This patient had moderate hematuria and hyperglycemia at 8 days, assessed as not related to study drug. It is not clear what was responsible, however.

One case of pseudothrombocytopenia occurred (assessed by a drop in EDTA counts but not in the citrated counts). It is noted by the sponsor that platelets swell in EDTA, causing the pseudothrombocytopenia. This is not seen when the sample is citrated.

C. Bleeding
There were 18 events in 8 patients after the first injection; there were 11 events in 9 patients after the second injection (see Table 8) Most (12 of 18 events after the first injection, 7 of 11 events after the second injection) were mucosal, lasting less than 5 minutes, mild, and no treatment was required. None were serious.

Bleeding sites involved nosebleeds, gingiva, and hematomata, ecchymoses and petechiae after both the first and the second injection. The onset of bleeding was during administration in most cases, ranging from within 11 minutes after injection to 9 and 11 hours after injection.

Bleeds were increased in patients < 70 kg who were treated with the non -weight adjusted infusion. Of the 17 subjects< 70 kg, 5 experienced bleeding after the initial injection; 3 in the non-weight adjusted and 2 in the weight adjusted group. (see Tables 9a and 9b)

D. Anticoagulation parameters
No notable changes were reported in PT or in aPTT after Abciximab injection. The median values were similar pre and post injection.

E. Thrombin Generation
No significant changes were observed in thrombin generation pre and post injection. The sponsor concludes that any changes were below the level of sensitivity of the assay, and that it is likely the subjects in this study would not have observable changes, as they were not in a state in which coagulation would be activated.

See Tables 8 and 9a and 9b on the following pages.

Table 8
SUBJECTS WITH ACUTE BLEEDING EVENTS

	All Subjects (n=41)	Subjects Who Were Reinjected (n=29)	
	Initial Injection	Initial Injection	Reinjection
Subjects with events	8 (20%)	4 (14%)	6 (21%)
Mucosal bleeding (gingival, nasal)			
Subjects with events	6 (15%)	3 (10%)	3 (10%)
Requiring pressure/packing	0	0	1 (3%)
Duration >5 min	0	0	1 (3%)
Onset after administration	3 (7%)	1 (3%)	2 (7%)
Superficial bleeding (hematoma, ecchymosis, petechiae, catheter site)			
Subjects with events	4 (10%)	1 (3%)	4 (14%)
Requiring Pressure/packing Treatment	3 (7%)	1 (3%)	2 (7%)
Hematoma >5cm	3 (7%)	1 (3%)	0
Onset after administration	2 (5%)	0	3(10%)

Table 9 a
NUMBER OF SUBJECTS WITH ACUTE BLEEDING EVENTS
BY DOSE GROUP

	Total	Body Weight ≤ 70 kg		70 to 80 kg		≥ 80 kg
		Wt-Adj	Non-Wt-Adj	Wt-Adj	Non-Wt-Adj	Non-Wt-Adj
Initial Injection	(n=41)	(n=9)	(n=8)	(n=8)	(n=8)	(n=8)
Subjects with Acute Bleeding Events	8 (20%)	2 (22%)	3 (38%)	0	1 (12%)	2 (25%)
Reinjection	(n=29)	(n=7)	(n=3)	(n=6)	(n=5)	(n=8)
Subjects with Acute Bleeding Events	6 (21%)	0	1 (33%)	2 (33%)	1 (20%)	2 (25%)

Table 9 b
NUMBER OF SUBJECTS WITH ACUTE BLEEDING EVENTS
BY WEIGHT GROUP

	Total	Body Weight ≤ 70 kg	70 to 80 kg	≥ 80 kg
Initial Injection	(n=41)	(n=17)	(n=16)	(n=8)
Subjects with Acute Bleeding Events	8 (20%)	5 (29%)	1 (6%)	2 (25%)
Reinjection	(n=29)	(n=10)	(n=11)	(n=8)
Subjects with Acute Bleeding Events	6 (21%)	1 (10%)	3 (27%)	2 (25%)

V. Sponsor's Conclusions

The sponsor concludes the following:

• The HACA assay yielded a higher than expected rate of positive responses in this trial: 5 of 41 subjects (12.2 %) after the first injection and 7 of 29 subjects (24 %) after the second injection. The larger clinical trials (EPIC, EPILOG and CAPTURE) have yielded only a rate of 5.1 to 6.5 % positive HACA responses. The same assay was used in this trial as in the others. The sponsor does not provide an explanation for this other than the small sample size in this trial compared to the others, or perhaps that the population in this trial is not representative of the patients who have received Abciximab in the large interventional trials.

• The safety of Abciximab is not altered upon retreatment (in HACA-HAMA non-responder patients), as 28 of 29 patients received reinjection without adverse events. There were no reports of anaphylaxis or allergic reactions in the study. Of the subjects with positive immune responses, only one exhibited an adverse event which was attributed to an immune response. This occurred after the second injection. That patient had thrombocytopenia occurring at 8 days after the second injection, concomitant with a rise in HAMA titer. Although the decrease in platelets was severe, the event resolved spontaneously.

• One other case of thrombocytopenia occurred in the study. This was a patient who had an immediate drop in platelets after the first dose was received. That patient was one of 8 who had a positive HACA response (low) prior to treatment. It was not felt that this was immune mediated, however, the investigators were uncertain of the mechanism that caused the thrombocytopenia in this case.

VI. Spontaneous Reporting (MedWatch) Data

Review has been completed of data on allergic phenomena reported through the spontaneous reporting (MedWatch) system in patients receiving commercial ReoPro since the marketing of the drug in December 1994. Four reports of allergic phenomena have been received, with ReoPro listed as one of the suspect medications. In all reports the patients were also receiving IV heparin, aspirin, and a contrast dye agent. Symptoms reported included shaking chills (3) , fever (2) , hypotension (2), skin rash (1), mucosal bleeding (1) and thrombocytopenia (1). One patient also developed pulmonary edema/ an ARDS syndrome. No data were available with these reports on HACA or HAMA antibody levels, or previous exposure to ReoPro. One patient was noted as having undergone PTCA x 2 previously, one within the previous 10 months.

VII. Reviewer Conclusions

1. It is unclear why the proportion of patients developing an immune response in this study is higher than that seen in the larger clinical trials. The same assay was used for all studies. It does not appear to be due to the more frequent sampling in this study; the patients in the larger trials were only drawn at 4 and 12 weeks, (30 days and 6 months in the EPILOG trial). If patients in this trial had been sampled at only 4 weeks and 12 weeks after each injection, there would have been 4 of 41 or 10 % with a positive HACA at 4 weeks and at 12 weeks after the first injection, and 6 of 29, or 22 %, at 4 weeks and 7 of 29, or 24 % at 12 weeks, after the second injection. These percentages are still higher than those seen in the larger clinical trials, which found a positive HACA rate of 5.1 to 6.5 %. However, there were more missing values in the patients studied in each of the larger trials than in this study. It is possible the missing values may have contributed. Based on the small sample

size in this study, the rate of 10% with a response after the first injection may not be substantially different than the rates seen in the larger studies. After the second injection, the rate of positive responses appears to be doubled, however.

2. There is a suggestion from this study that the antibody response after readministration of Abciximab occurs earlier and to a higher titer than after the first injection, and in a larger proportion of patients.

3. It is reassuring to see that there is no evidence of increased rates of clearance of Abciximab or of alterations in pharmacodynamics with reinjection of patients without prior antibody responses. Thus the dose regimens proposed for initial administration may be used for readministration of Abciximab without diminution of effect in patients without a demonstrable HACA or HAMA response.

4. There is a concern that the development of antibodies relevant to the this type of monoclonal therapy may have significant adverse clinical consequences. There is no evidence of allergic or anaphylactic reaction to the agent in this study or in the larger clinical studies; a total of 3,900 patients have been treated with Abciximab. However, events that may occur with very low frequency may not yet be apparent. The data from the MedWatch reports raise some concern; however, the reactions reported may be attributable to other medications the patients had received, including contrast dye, in at least some of the reports, and suggest that close monitoring for such phenomena be a part of any further studies with Abciximab.

5. There are insufficient data at this point to adequately predict the immune response or the clinical consequences in patients who are reinjected and have had a positive antibody response. With the limited data gathered thus far, there have not been any cases of severe allergic or anaphylactic responses in patients reinjected (in the clinical studies). However, only antibody negative patients have been reinjected in the studies.

From data in this trial on repeat percutaneous interventions, it can be expected that 20 to 25 % of patients treated initially may have need for repeat administration of Abciximab within the following 6 months. This percentage is likely to increase over the following year(s), as the drug does not appear to retard the progression of atherosclerotic disease, and a given patient may have recurrent thrombotic episodes. From data in this study, 25 % of patients may have a positive antibody response after the second injection. It is thought that the anamnestic response following readminstration of antigenic substances increases the likelihood of serious clinical consequences of readminstration. The treatment effect of this drug has been shown to be 5 to 8 %. If the clinical effects of the development of antibodies to the drug are significant, the risk of treatment approaches the size of the benefit after repeat adminstrations. The development of antibodies to Abciximab and allergic phenomena after readministration should be assessed in patients who are antibody positive.

6. There is one case of thrombocytopenia in this study the sponsor attributes as immune-mediated. The clinical significance of this one case is unclear. Thrombocytopenia following Abciximab administration has occurred sporadically in the larger trials; the mechanism(s) responsible have not been elucidated.

7. This reviewer agrees with the sponsor's conclusions regarding thrombin generation in this study. This information would be interesting to see in patients receiving anticoagulation and being treated for active thrombus formation.